PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Vijay Kumar HANDA et al.

Group Art Unit: 1624

Application No.: 10/688,606

Examiner: M. Berch

Filed: October 17, 2003

Publication No.: US 2005/0043531 A1

Publication Date: February 24, 2005

For: PROCESS FOR PREPARING CEFEPIME

THIRD PARTY SUBMISSION UNDER 37 CFR 1.99

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 CFR 1.99, submitted herewith are "patents or publications relevant to a pending published application."

Specifically, attached hereto is a copy of each of:

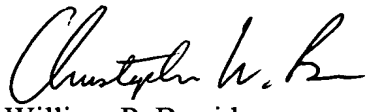
1. WO 2004/058695 A1 (published July 15, 2004);
2. U.S. Publication No. 2003/0199712 A1 (published October 23, 2003);
3. WO 2004/092183 (published October 28, 2004);
4. U.S. Patent No. 5,109,131 (issued April 28, 1992);
5. U.S. Patent No. 6,384,215 (issued May 7, 2002); and
6. WO 00/63214 (published October 26, 2000).

This submission is timely filed, having been filed within two months of the February 24, 2005 publication date of US 2005/0043531 A1.

In compliance with 37 CFR 1.99(b), submitted herewith is (1) the fee set forth in 37 CFR 1.17(p) (check no. 164965 ($180.00)); (2) a list of each patent or publication, including the date of publication (set out above); and (3) a copy of each listed patent or publication.

Also, in compliance with 37 CFR 1.99(c), submitted herewith is proof of service in accordance with 37 CFR 1.248.

Respectfully submitted,



William P. Berridge
Registration No. 30,024

Christopher W. Brown
Registration No. 38,025

WPB:CWB/rav

Date: March 23, 2005

Attachments:
Patents and Publications Listed Above (6)
Check No. 164965 ($180)
Certificate of Service

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of this paper (and any papers referred to herein as being attached or enclosed) is today being sent by first class mail to Jay R. Akhave, 845 Pomello Drive, Claremont, California 91711, identified as attorney/agent of record for the applicants in the U.S. Patent Office's application file.

March 23, 2005
Date

Christopher W. Brown

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 July 2004 (15.07.2004)

PCT

(10) International Publication Number
WO 2004/058695 A1

(51) International Patent Classification[7]: C07C 305/00, 303/24, C07D 501/00

(21) International Application Number:
PCT/IN2002/000245

(22) International Filing Date:
26 December 2002 (26.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **LUPIN LIMITED** [IN/IN]; 159 C.S.T. Road, Kalina, Santacruz (East), Mumbai 400 098, Maharashtra (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DATTA, Debashish** [IN/IN]; Lupin Limited (Research Park), 46A/47A, Nande Village, Taluka Mulshi, Pune 411 042, Maharashtra (IN). **DANTU, Muralikrishna** [IN/IN]; Lupin Limited (Research Park), 46A/47A, Nande Village, Taluka Mulshi, Pune 411 042, Maharashtra (IN). **MISHRA, Brijkishore** [IN/IN]; Lupin Limited (Research Park), 46A/47A, Nande Village, Taluka Mulshi, Pune 411 042, Maharashtra (IN). **SHARMA, Pollepeddi, Lakshmi, Narayana** [IN/IN]; Lupin Limited (Research Park), 46A/47A, Nande Village, Taluka Mulshi, Pune 411 042, Maharashtra (IN).

(74) Agents: **MAJUMDAR, S.** et al.; S. Majumdar & Co., 5, Harish Mukherjee Road, Calcutta 700 025 (IN).

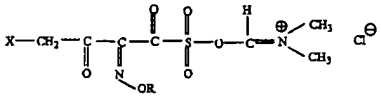
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

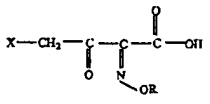
Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

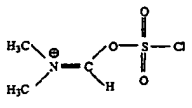
(54) Title: NOVEL INTERMEDIATES FOR SYNTHESIS OF CEPHALOSPORINS AND PROCESS FOR PREPARATION OF SUCH INTERMEDIATES



(I)



(IV[1])



(VII)

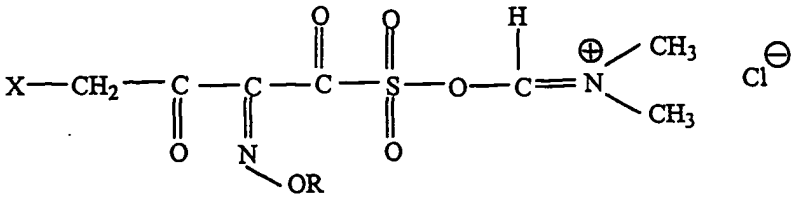
(57) Abstract: A novel 4-halo-2-oxyimino-3-oxo butyric acid-N, N-dimethyl formiminium chloride chlorosulfate of formula (I) useful in the preparation of cephalosporin antibiotics, wherein X is chlorine or bromine; R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$, wherein R_5 is hydrogen or an easily hydrolysable ester group. The compound of formula (I) is prepared by reacting 4-halo-2-oxyimino-3-oxobutyric acid of formula (IV^1), wherein X, R and R_5 are as defined above, with N, N-dimethylformiminium chloride chlorosulphate of formula (VII), in an organic solvent at a temperature ranging from -30 °C to -15 °C. The cephalosporins that may be prepared from the intermediate include cefdinir, cefditoren pivoxil, cefepime, cefetamet pivoxil, cefixime, cefmenoxime, cefodizime, cefoselis, cefotaxime, cefpirome, cefpodoxime proxetil, cefquinome, ceftazidime, cefteram pivoxil, ceftiofur, ceftizoxime, ceftriaxone and cefuzonam.

WO 2004/058695 A1

NOVEL INTERMEDIATES FOR SYNTHESIS OF CEPHALOSPORINS AND PROCESS FOR PREPARATION OF SUCH INTERMEDIATES

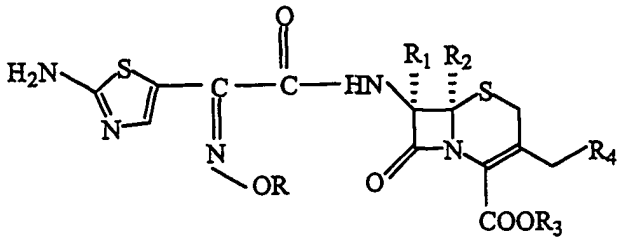
FIELD OF THE INVENTION

The present invention relates to novel compounds of formula (I),



(I)

wherein X is chlorine or bromine; R is hydrogen, , C_{1-4} alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$, wherein R_5 is hydrogen, or an easily hydrolysable ester group. The present invention also relates to a process for preparation of the compounds of formula (I). The invention also relates to the use of the novel compounds of formula (I) for preparation of cephalosporin antibiotics, in particular cephalosporin compounds of formula (II).



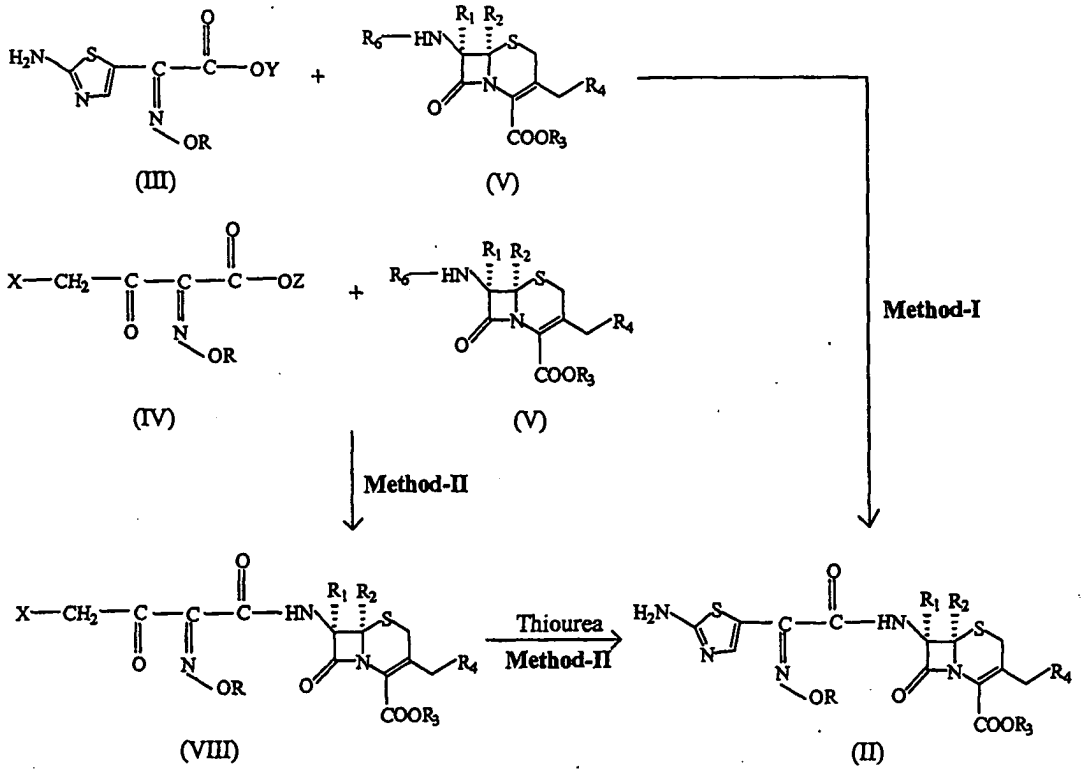
(II)

wherein R and R_5 are as defined above; R_1 is hydrogen or $-OCH_3$; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal ; R_4 is hydrogen or is a substituent useful in cephalosporin chemistry.

BACKGROUND OF THE INVENTION

Cephalosporin compounds of formula (II) are generally synthesised by two methods as described in the art. Both the methods involve amidification of the 7-amino function of the corresponding 3-(un)substituted cephalosporin derivative either directly with a 2-(2-amino

thiazol-4-yl)-2-oxyimino acetic acid derivative (**Method-I**) or via **Method-II** a 4-halo-2-oxyimino-butyric acid derivative to give a 7-substituted cephalosporin addendum, which can be further elaborated to form the 2-(2-amino thiazol-4-yl)-2-oxyimino acetamido side chain and thereby, provide compounds of formula (II). The two methods of synthesis are summarized in **Scheme -I.**



R is hydrogen, C_{1-4} alkyl, $-CH_2COOR_5$ or $-C(CH_3)_2COOR_5$ R_5 is hydrogen, an easily hydrolysable ester group X is Cl or Br R_1 is hydrogen or OCH_3 ; R_2 is hydrogen ; R_3 is hydrogen, a negative charge or together with the CO group to which R_3 is attached is an ester or an alkali or alkaline earth metal R_4 is hydrogen or is a substituent useful in cephalosporin chemistry R_6 is hydrogen or silyl

SCHEME-I : Prior Art methods for Synthesis of Compounds of Formula (II)

In compounds of formula (III) of **Method-I**, the meanings of the groups X and R are as defined hereinearlier and the group Y is hydrogen or is a group which forms a basis that compound of formula (III) is in a reactive form. Similarly, in compound of formula (IV), of **Method-II**, the meanings of the groups X and R are as defined hereinearlier and the group Z is hydrogen or is a group which forms a basis that compound of formula (IV) is in a reactive form.

As per **Method-I**, synthesis of compound of formula (II) has been achieved by several ways, all differing in the choice of the reactive group Y. The following prior art methods illustrate the

synthesis of compounds of formula (II) utilizing different reactive species as embodied in the group Y. These are to name a few;

i) US Patent No. 4 152 432 describes synthesis of cefotaxime comprising acylation of 7-aminocephalosporanic acid (7-ACA) with a compound of formula (III), wherein R is methyl and Y is a chlorine atom. In this method, the amino group of the thiazole ring is protected prior to amidification and subsequently deprotected by hydrolysis or hydrogenolysis.

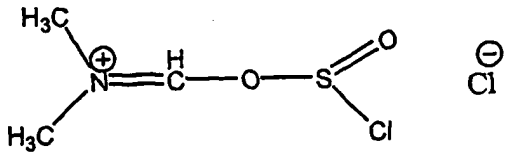
Japanese Patent Nos. JP 52-102096, JP 53-157596 and British Patent No. GB 2 025 933 also utilize the same chemistry mentioned hereinbefore i. e. activation of the carboxylic acid as the acid halide. The acid halide, in particular the acid chloride is prepared by reaction of the 2-(2-amino thiazol-4-yl)-2-oxyimino acetic acid with PCl_3, PCl_5, $SOCl_2$ or $POCl_3$.

US Patent No. 3 954 745 also teaches a method for synthesis of cefazolin via the acid chloride method.

ii) Another method of activation of the carboxylic acid of formula (III), as disclosed in US Patent No. 5 317 099 is through formation of the activated ester by reaction of the carboxylic acid group with an acyloxyphosphonium chloride derivative. The method of preparation comprises reacting the carboxylic acid derivative (III) with triphenyl phosphine, hexachloroethane or carbon tetrachloride. However, this method increases the overall cost of the coupling reaction since it involves the use of expensive triphenyl phosphine.

iii) EP Patent Nos. EP 0 037 380 describes yet another method for synthesis of compounds of formula (II), specially cefotaxime and ceftriaxone, wherein the carboxylic acid group of compound (III) is activated as the benzothiazolyl thioester prior to formation of the amide bond at the 7-amino position. The benzothiazolyl thioester is turn prepared by reaction of the carboxylic acid compound (III) with bis[benzothiazolyl-(2)]disulfide and triphenyl phosphine, thereby rendering the method costly.

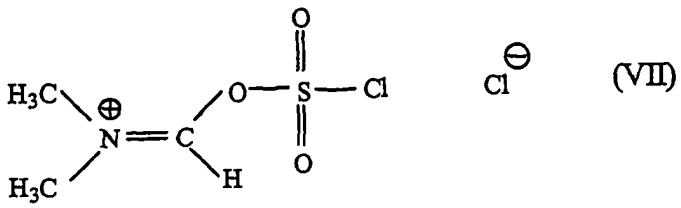
iv) US patent No. 5 037 988 describes a process for production of compounds of formula (II), in particular, cefotaxime and ceftriaxone, in which the 2-(2-amino thiazol-4-yl)-2-oxyimino acetic acid (III) is activated as the dimethyl formiminium chloride chlorosulfite (DFCS) of formula (VI) and then coupled at the 7-amino position of the 3-substituted cephalosporin derivative to give compounds of formula (II).



(VI)

The dimethyl formiminium chloride chlorosulfite (VI), is in turn prepared by reacting equimolar quantities of thionyl chloride and N, N-dimethylformamide at room temperature. The method however, suffers from drawbacks inter alia in that the reaction can be effected in only specific solvents like benzene and toluene.

v) US Patent No. 5 739 346 describes a process for synthesis of β-lactam derivatives such as cefotaxime and ceftriaxone wherein compound (III) is activated as an adduct with N, N dimethyl formiminium chloride chlorosulfite (DFCCS) of formula (VII), prior to 7-amidification to give compounds of formula (II).



(VII)

vi) WO 99/51607 discloses a process for preparation of cefixime, wherein 7-amino-3-vinyl-3-cephem-4-carboxylic acid is reacted with compound (III) activated as the benzothiazolyl thioester.

vi) US Patent No. 6 388 070 provides yet another variation, wherein the compound (III) is activated as a 2-mercapto-5-substituted-1, 3,4-oxadiazole derivative prior to 7-amidification to give compounds of formula (II).

The amidification has also been achieved by activation of the carboxylic acid (III) by formation of its mixed anhydride, an active amide or an active ester, as disclosed in US Patent No. 4 409 214; as the thiophosphoryl ester, as disclosed in US Patent No. 5 567 813 for synthesis of cefixime, cefotaxime, ceftriaxone, cefepime, cefpirome sulfate, ceftizoxime etc.

Synthesis of compounds of formula (II) as per **Method-II** is equally widely documented in the literature. Several methods, varying subtly in the choice of the reactive group Z of compounds of formula (IV) have been utilised, albeit the choice of the activating group is primarily restricted to acid halides. A few of such methods are disclosed in :

a) US Patent No. 4 559 334, discloses a method for synthesis of cefdinir, wherein the carboxylic acid (IV) activated as the acid chloride is reacted with 7-amino-3-vinyl-3-cephem-4-carboxylic acid to give the 7-substituted addendum, which on reaction with thiourea gives cefdinir.

b) US Patent No. 4 409 214 discloses a method identical for synthesis of cefixime, a structurally similar analogue of cefdinir.

c) US Patent No. 5 109 131 describes an advantageous process for preparation of cephalosporin compounds using tert-butyl-3-oxobutyrate as an intermediate. The tert-butyl-3-oxobutyrate is used for preparation of the compound (IV), which is reacted as such or a reactive derivative thereof is reacted with a 3-substituted-7-amino cephalosporin compound to form the 7-substituted cephalosporin addendum, which on reaction with thiourea gives compounds of formula (II).

The reactive derivatives utilised for 7-amidification as disclosed in US Patent No. 5 109 131 include acid halides, a mixed acid anhydride, an active amide or an active ester.

c) European Patent No. 0 030 294 discloses a method for preparation of ceftriaxone comprising reaction of 4-bromo-2-methoxyimino-3-oxobutyric acid chloride with 7-amino-3-desacetoxy-3-[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)-thio]-3-cephem-4-carboxylic acid to give the 7-amino addendum, which is cyclized with thiourea to give ceftriaxone.

d) European Patent No. 0 842 937 claims a process for preparation of cefotaxime and ceftriaxone comprising reaction of 7-ACA and 7-amino-3-desacetoxy-3-[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)-thio]-3-cephem-4-carboxylic acid respectively with 4-chloro-2-methoxyimino-3-oxobutyric acid, activated as 2-mercaptobenzothiazolyl ester, followed by cyclisation of the intermediates thus obtained with thiourea to give cefotaxime and ceftriaxone respectively.

e) US Patent No. 4 960 766 discloses a method for acylation at the 7-amino position of a 3-substituted cephalosporin derivative by reaction with compound (IV), which is activated as an acid halide or as a mixed anhydride, an activated amide or an activated ester in the presence of dicyclohexylcarbodiimide or an organic or inorganic base to give the corresponding acylated compound. Formation of the thiazolyl ring is completed when the acylated compound thus obtained is reacted with thiourea.

f) EP Patent No. 0 556 768 describes a method for preparation of ceftriaxone comprising reaction of 7-amino-3-desacetoxy-3-[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)-thio]-3-cephem-4-carboxylic acid with 4-chloro-2-methoxyimino-3-oxobutyric acid, activated as 2-mercaptobenzothiazolyl ester, followed by cyclisation of the intermediate thus obtained with thiourea to give ceftriaxone . This patent claims that the abovementioned reaction and subsequent conversion of ceftriaxone to its disodium hemiheptahydrate salt can be carried out in one pot using a mixture of acetone and water as solvent.

g) US Patent No. 6 384 215 provides yet another variation, wherein the compound (Iv) is activated as a 2-mercapto-5-substituted-1, 3,4-oxadiazole derivative prior to 7-

amidification to give compounds of formula (II) after cyclisation of the intermediate compound with thiourea.

h) US Patent No. 6 458 949 discloses a process for preparation of ceftiofur by reacting silylated 7-amino-3-(2-furylcarbonylthiomethyl)-3-cephem-4-carboxylic acid with 4-bromo/chloro-2-methoxyimino-3-oxobutyryl acid halide, followed by cyclization of the compound thus formed with thiourea.

i) Published US Patent Application No. 2002/0128469 A1 claims an improved method for preparation of compounds of formula (II), specially cefotaxime and ceftriaxone comprising reaction of compound (V, see **Scheme-I**) with compound (IV) activated as a reactive derivative to give the corresponding intermediate 7-acylated compound, the improvement being reaction of the intermediate 7-acylated compound thus obtained is cyclized with silylated thiourea to form the aminothiazole ring.

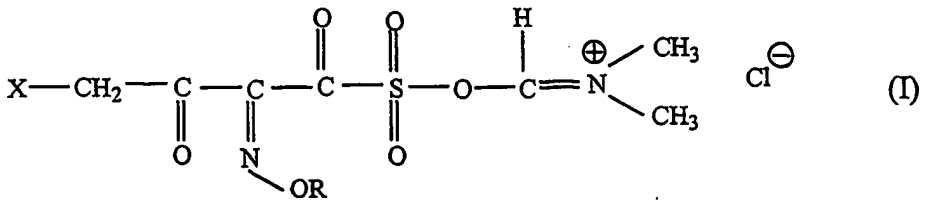
Surprisingly, the present inventors have found a novel manner of activation of the carboxylic acid of 4-halogeno-2-oxyimino-3-oxobutyric acid of formula (IV), which provides novel reactive derivatives of formula (I).

Thus, it is an object of the present invention to provide novel reactive derivatives of formula I.

Yet further object of the present invention is to provide a simple and cost-effective method for preparation of cephalosporin compounds of formula (II) utilising compounds of formula (I).

SUMMARY OF THE INVENTION

Thus the present invention according to one aspect provides novel compounds of formula (I)



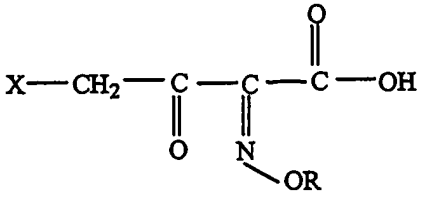
(I)

wherein X is chlorine or bromine;

R is hydrogen, C $_{1-4}$ alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$, wherein

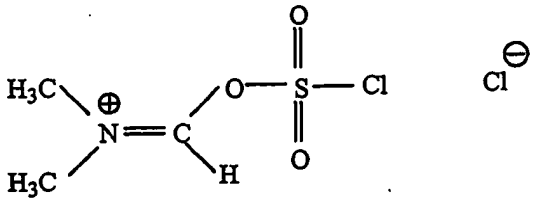
R_5 is hydrogen, or an easily hydrolysable ester group.

According to another aspect of the present invention there is provided a method for preparation of compounds of formula (I) comprising reaction of 4-halo-2-oxyimino-3-oxobutyric acid of formula (IV^1),



(IV^1)

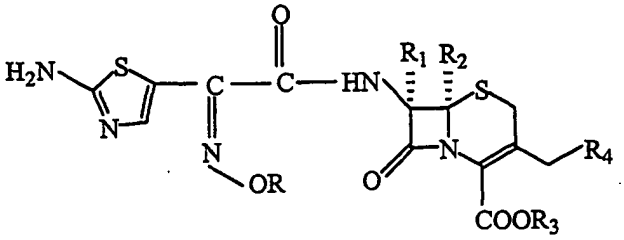
wherein X and R are as defined hereinbefore with N, N-dimethylformiminium chloride chlorosulphate of formula (VII)



(VII)

in an organic solvent at a temperature ranging from -30^0 C to -15^0 C.

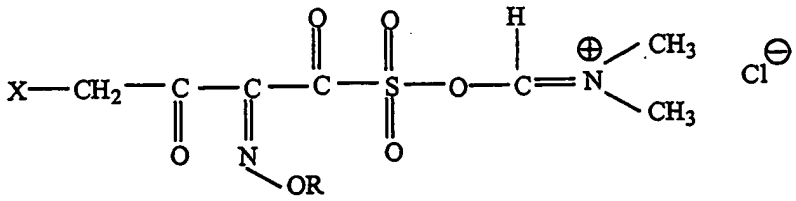
According to a further aspect of the present invention there is provided a process for preparation of cephalosporin compounds of formula (II)



(II)

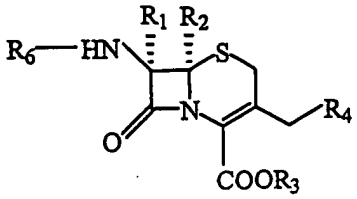
wherein R and R_5 are as defined above; R_1 is hydrogen or $-OCH_3$; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester or an alkali or alkaline earth metal; R_4 is hydrogen or is a substituent useful in cephalosporin chemistry,

the process comprising reaction of compound of formula (I)



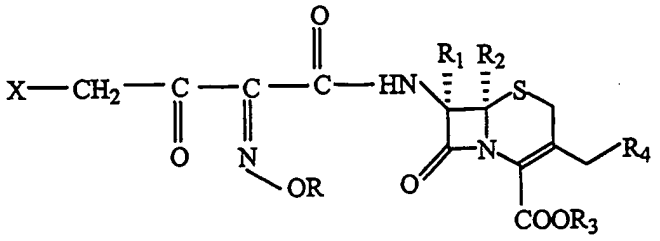
(I)

wherein X and R are as defined hereinbefore with 7-amino cephalosporanic acid of formula (V),



(V)

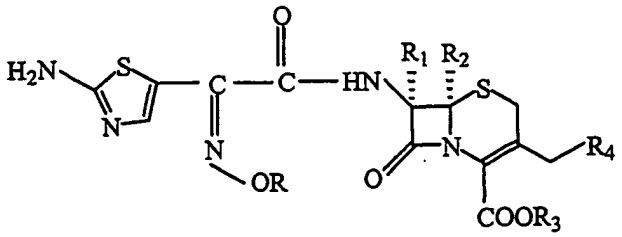
wherein R_1 is hydrogen or $-OCH_3$; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal, or is a silyl group; R_4 is hydrogen or is a substituent useful in cephalosporin chemistry; and R_6 is hydrogen or a silyl group with the proviso that, when R_3 is hydrogen R_6 is also hydrogen; when R_3 is a silyl group R_6 is also a silyl group; and when R_3 is an ester, or an alkali or alkaline earth metal R_6 is hydrogen to give 7-[(4-halo-2-oxyimino-3-oxobutyramido-3-substituted-3-cephem-4-carboxylic acid of formula (VIII),



(VIII)

wherein X, R, R_1, R_2 and R_4 have the same meanings as defined hereinearlier and R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal,

followed by cyclisation of compound (VIII) with thiourea to give compounds of formula (II),



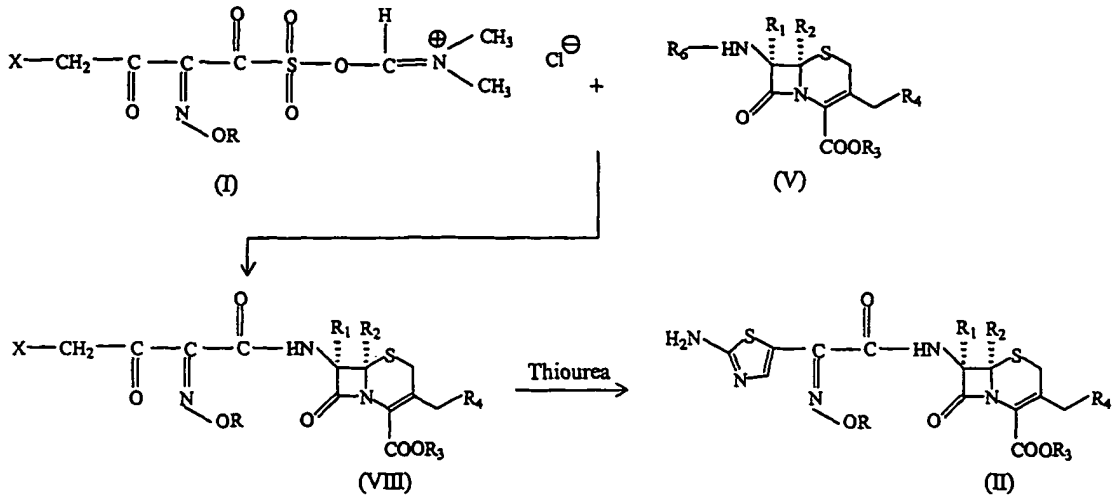
(II)

wherein R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$, wherein R_5 is hydrogen, or an easily hydrolysable ester group; R_1 is hydrogen or $-OCH_3$; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester or an alkali or alkaline earth metal; and R_4 is hydrogen or is a substituent useful in cephalosporin chemistry.

The group R_4, which is a substituent useful in cephalosporin chemistry includes *inter alia* those substituents which are conventional in cephalosporin chemistry and which are useful in pharmaceutically active cephalosporins and thus include unsubstituted and substituted alkyl; unsubstituted and substituted alkenyl; alkyl and an alkenyl substituted by alkoxy, heterocyclthio, heterocycylcarbonylthio, alkylcarbonyloxy and heterocycyl. Heterocycyl includes 5 or 6 membered heterocycyl including a bicyclic ring system having 10 to 12 carbon atoms; a heterocycyl having 1 to 4 hetero atoms, selected from N, O or S.

DETAILED DESCRIPTION OF THE INVENTION

The process for the preparation of the compound of formula II the chemistry of which is summarized in reaction **Scheme-II**.



(I) (V) (VIII) (II)

REACTION **SCHEME-II : Method of Synthesis of Compounds (II) as per the Present Invention**

The abovementioned aspects of the present invention are illustrated hereinbelow in greater details.

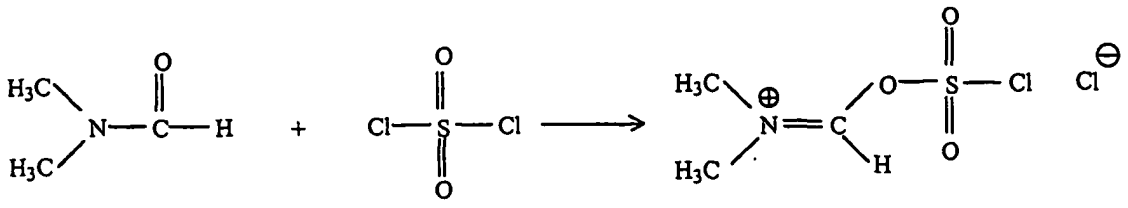
1) Preparation of N, N dimethyl formiminium chloride chlorosulfite (DFCCS)(VII)

DFCCS (VII) is a known compound and described in the literature, viz. *Z.Chem*, 6 (4), 148 (**1996**); *J.C.S. Perkin Trans I*, 2004-2007 (**1972**); *Bull. Chem. Soc. Jpn.*, 58, 1063-1064; *Adv Org Chem.*, 9 (2), 5, (**1979**); *Synthetic Reagents*, Vol. 4, 388-389; *Angew Chem. Internal. Edit.*, 1 (12), 647 (**1962**); US Patent Nos. 5 739 346; 5 856 502; 5 945 532 and EP Patent No. 0 791 597.

While DFCCS (VII) prepared by any known process might be used, the inventors have found that best results are obtained when DFCCS (VII) is prepared by the following process.

The preferred process for obtaining the DFCCS (VII) comprises adding sulfuryl chloride to N, N-dimethylformamide at –20 ^{0}C. The temperature is raised to 0 ^{0}C at which the solid adduct crystallized out, which is vigorously stirred at for one hour, followed by addition of dichloromethane to the resulting reaction mixture. The temperature was raised to 15 ^{0}C to 20 ^{0}C and at this temperature the solid crystals melt, resulting in the formation of an immiscible layer of the desired adduct, i. e. (VII).

Such mode of preparation of DFCCS (VII) is illustrated in **Scheme III**.



DFCCS(VII)

SCHEME-III : Method for preparation of DFCCS (VII)

The DFCCS (VII) adduct thus obtained by the preferred process of the invention is found to be advantageous in use in the process of manufacture of the reactive derivatives of formula I in accordance with the objective of the invention for the reasons given below:

i) Unlike the complex, viz. dimethyl formiminium chloride chlorosulfite (DFCS) of formula (VI) utilized in the prior art, DFCCS (VII) used in the process of the present invention remains stable and does not get converted to the normal Vilsmeier's reagent. It has been observed that DFCCS (VII) of the present invention is apparently more stable than DFCS (VI), described in US Patent No. 5 037 988. In particular, it is found that the thus obtained DFCCS (VII) used in the process of the invention is distinct from thionly chloride-DMF adduct, i.e., dimethylformiminium chloride chlorosulfite (DFCS, VI) known in the art. The melting point of the latter is 138 ^{0}C-140 ^{0}C [*Helv. Chim. Acta.*, 62, 1655 (**1959**)] while that of DFCCS (VII) is 40 ^{0}C – 41 ^{0}C [*Z..Chem.*, 6 (4), 148 (**1966**)].

ii) The DFCCS (VII) used in the process of the invention can be prepared in any solvent such as benzene, toluene, acetonitrile or dichloromethane, and preferably, in the absence of solvents. This is advantageous and clearly distinct from the thionly chloride-DMF adduct, i.e., dimethyl formiminium chloride chlorosulfite (DFCS, VI) described in US Patent No. 5 037 988, which cannot be prepared in solvents such as chloroform or dichloromethane, since these solvents facilitate complete or partial conversion of dimethyl formiminium chloride chlorosulfite to normal Vilsmeier's reagent.

iii) It has been found that sulfuryl chloride-DMF adduct DFCCS of formula (VII) is more stable than DFCS (VI), made from thionly chloride and DMF. Thus, when DFCCS (VII) was kept at ambient temperature for 16 hours and used for further complexion with compounds of formula (V) for synthesis of the activated ester required for the final acylation reaction, the drop in yield for the final antibiotics was about 26% (85% when used fresh and 59% after storage of DFCCS for 16 hrs.). Similarly when DFCS adduct was kept at ambient temperature for 16 hrs. and further processed for synthesis of the final antibiotic, the drop in yield was about 35% (80% when used fresh and 45% when used after 16 hours). Hence, DFCCS obtained by the preferred process described above has superior stability compared to DFCS adduct of formula (VI).

Thus, the use of DFCCS (VII) for synthesis of the compound of formula (I), provides a practical, cost effective and safe method for manufacture of the desired cephalosporin antibiotics of formula (II).

*2) **Preparation of Novel Compounds of formula (I):***

The reactive compounds of formula (I) is prepared by the reaction of 4-halo-2-methoxy imino butyric acid (IV^1) and N, N-dimethyl formiminium chloride chlorosulfate i.e., DFCCS (VII) as obtained from **Scheme -III**.

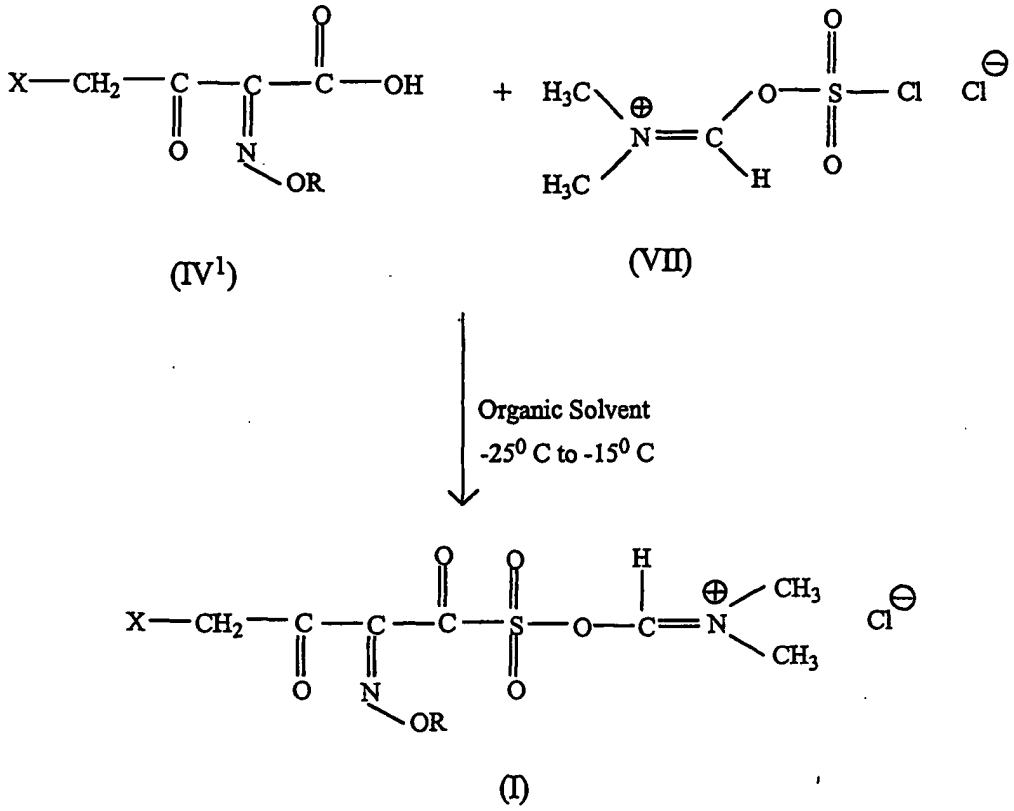
In a typical reaction, DFCCS (VII) is added to 4-halo-2-oxyimino-3-oxo butyric acid (IV^1) in an organic solvent at a temperature of -25^0 C to $-15\ ^0$ C and thereafter, the reaction mixture is stirred for two hours at a temperature of 5-10 ^{0}C. The compound of formula (I) thus obtained can be stored at low temperature for a period of 3-6 hrs before use in the next step.

The process is summarized in **Scheme-IV**.

Any organic solvent can be used in the reaction for formation of compounds of formula (I). However, the formation of compound (I) is best prepared in chlorinated solvents selected from dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons selected from

benzene and toluene; and nitrile solvents selected from acetonitrile, propionitrile and butyronitrile. However, chlorinated hydrocarbons are more preferred and among these dichloromethane is the preferred solvent.

The DFCCS (VII) is employed in molar to slightly more than molar proportions to the carboxylic acid compound (IV^1) used. Preferably, the molar ratio of the DFCCS (VII) to the carboxylic acid of formula (IV^1) is between 1.1 to 1.3.



(IV^1) (VII)

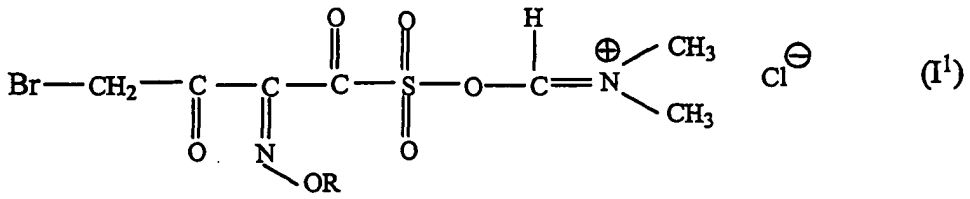
(I)

SCHEME-IV : Method of preparation of Compounds of formula (I)

As mentioned hereinearlier, compounds of formula (I) obtained by the reaction summarized in **Scheme-IV** are relatively stable than other mixed anhydrides and the adduct of the carboxylic acid (IV^1) with DFCS of formula (VI) on storage at low temperatures. The novel compounds of formula (I) can be stored for a time period of 3-6 hours below –20 ^{0}C.

The compounds of formula (I) exhibit distinct spectral properties as evidenced by their PMR, IR and Mass Spectra.

The PMR spectrum of the novel 4-bromo-2-methoxyimino-3-oxo butyric acid N, N dimethyl formiminium chloride chlorosulfite adduct of formula (I^1) was recorded neat with DMSo-d_6 as external lock at room temperature using CH_2Cl_2 as reference. The spectra shows two broad 1H signals at 13.4 ppm and 8.2 ppm respectively. Singlets due to $-BrCH_2$ and $-OCH_3$ are observed at 4.3 and 4.1 ppm respectively. The $-N(CH_3)_2$ signals appears at 3.2 and 3.1 ppm respectively.



(I^1)

The IR spectrum of the freshly prepared bromo compound (I^1) shows signals at 1784 cm^{-1} indicating anhydride functionality. After prolonged period of time, the signal disappears and a broad signal at 3379 cm^{-1} appears, implying that the anhydride is unstable and gets hydrolysed to the acid.

The mass spectrum of the bromo compound (I^1) using a non-protic solvent at room temperature shows a signal of weak intensity at m/z 397.5 amu in the +APCI mode of ionization, indicative of the existence of the species of formula (I^1).

The PMR, IR and Mass Spectra of the bromo compound (I^1) are reproduced in Fig-1, Fig-2 and Fig-3 respectively.

Of the chloro and bromo compounds of formula (I), the bromo compounds are preferred for use in synthesis of cephalosporin compounds of formula (II).

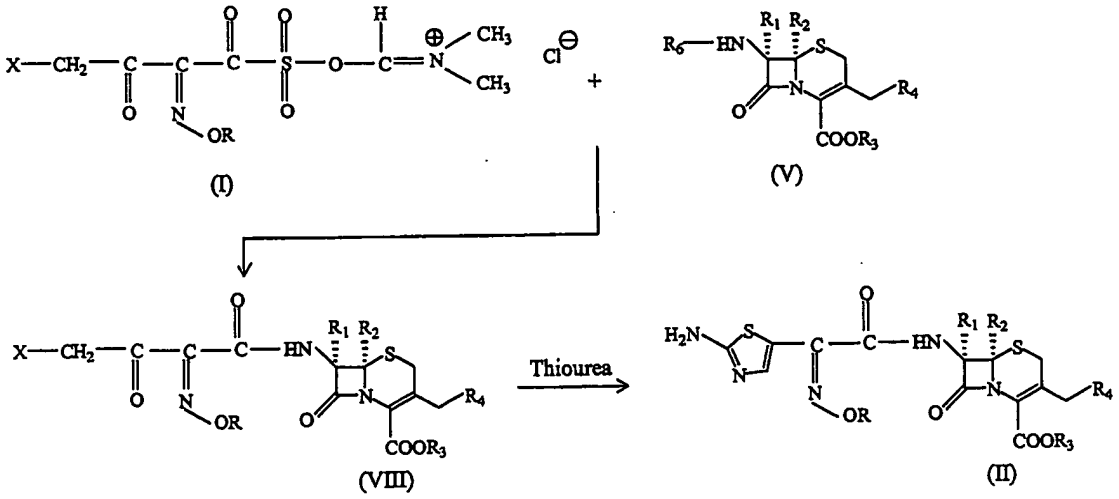
The carboxylic acid compounds of formula (IV^1) are known compounds and can be prepared in high purity and good yield starting from tert-butyl acetoacetate as described in US Patent No. 5 095 149 and US Patent No. 5 109 131.

3) ***Synthesis of cephalosporin compounds of formula (II) utilizing novel compounds of formula (I).***

The novel compounds of formula (I) are useful in the manufacture of valuable cephalsosporin antibiotics of formula (II), as per the method summarized in **Scheme-II**. The method provides a practical, cost-eefective and safe method for manufacture of the said cephalosporin antibiotics.

Compounds of formula (I) due to their inherent stability on storage are preferred over the other mixed anhydrides of the carboxylic acid (IV^1) or the adduct of the carboxylic acid (IV^1) with DFCS of formula (VI), which are somewhat less stable.

The process for manufacture of the desired cephalosporin antibiotics of formula (II) according the present invention basically involves the following steps, as summarized in **Scheme-II**.



SCHEME-II : Method of Synthesis of Compounds (II) as per the Present Invention

A. Reaction of compound of formula (I) with the corresponding 7-amino-3-substituted cephalosporonic acid of formula (V) to give the 7-amino addendum of formula (VIII), and

B. Reaction of the 7-amino addendum of formula (VIII) thus obtained with thiourea to give the cephalosporin antibiotics of formula (II).

In Step A of the process, the reactive compound (I) is treated with the 7-aminocephalosporanic acid of formula (V) in an organic solvent and in the presence of a base at a temperature ranging from -80^0 C to -15^0 C, preferably -55^0 C to -25^0 C yield the 7-amino addendum of formula (VIII).

In compounds of formula (V), R_1 is hydrogen or $-OCH_3$; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal, or is a silyl group; and R_4 is hydrogen or is a substituent useful in cephalosporin chemistry; R_6 is hydrogen or a silyl group with the proviso that, when R_3 is hydrogen R_6 is also hydrogen; when R_3 is a silyl group R_6 is also a silyl group; and when R_3 is an ester, or an alkali or alkaline earth metal R_6 is hydrogen

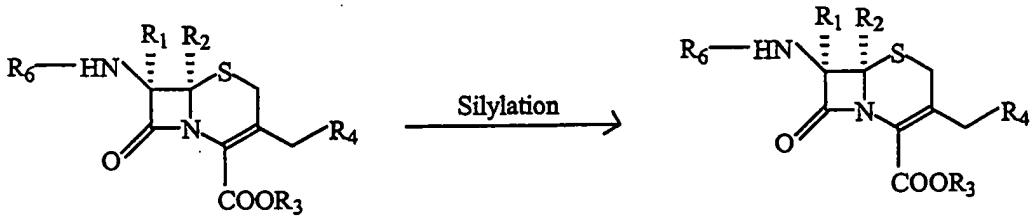
When R_3 is a negative charge, the group R_4 may contain a positive charge; e.g. in the form of a positively charged amine.

If R_3 together with the COO^- group to which it is attached is an ester group R_3 preferably forms with the COO^- group a physiologically hydrolysable and acceptable ester, e.g. R_3 is a substituent useful in cephalosporin chemistry.

By easily hydrolysable esters of the compounds of formula (II) it is to be understood compounds of the formula (II) in which the carboxyl group is present in the form of an ester group which can be easily hydrolysed. Examples of such esters, which can be of the conventional type, are the lower alkyl esters such as methyl, ethyl, tertiary butyl; alkanoyloxyalkyl esters, e.g. the acetoxy methyl, pivaloxymethyl, 1-acetoxyethyl, 1-pivaloxyethyl ester; the lower alkoxycarbonyloxyalkyl esters, e.g. the methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxyethyl ester; the alkoxymethyl esters, e.g. methoxy methyl ester, and the lower alkylaminomethyl esters, e.g. the acetamidomethyl esters. Other esters, e.g. the benzyl and cyanomethyl esters can also be used.

Alternatively, the compound of formula (V), in which R_3 and R_6 are hydrogen can be reacted with a silylating agent to effect silylation at the 4-carboxylic acid and the 7-amino position to form the corresponding (bis)-silylated compound of formula (V), wherein R_3 and R_6 are silyl groups, which is then reacted with the reactive compound (I) in an organic solvent and in the presence of a base at a temperature ranging from -80^0 C to -15^0 C, preferably -55^0 C to -25^0 C to yield the 7-amino addendum of formula (VIII).

The silylation of compound (V) can be achieved by conventional ways using conventional silylating agents such as hexamethyldisilazane, trimethylchlorosilane, bis (trimethyl) silylacetamide etc. The silylated compound (V), thus obtained without isolation can be reacted with compounds of formula (I) to give the 7-amino addendum of formula (VIII).



(V)
R_3 and R_6 is hydrogen

(V)
R_3 and R_6 is a silyl group

The basic compounds used as acid scavenging agent to capture HCl released during silylation include N, N dimethyl aniline, diethyl amine, pyridine, preferably N, N dimethyl aniline.

Any organic solvent can be used in the reaction for formation of compounds of formula (VIII). However, the formation of compound (VIII) is best carried out in chlorinated solvents selected from dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons selected from benzene and toluene; nitrile solvents selected from acetonitrile, propionitrile and butyronitrile; and ether solvents selected from tetrahydrofuran and dioxane. However, chlorinated hydrocarbons are more preferred and among these dichloromethane is the preferred solvent.

The compound (I) is employed in molar to slightly more than molar proportions to the cephalosporin compound (V) used. Preferably, the molar ratio of compound (I) to the cephalosporin compound (V) is between 1.1 to 2.0 and more preferably between 1.2 to 1.5.

Even though, both the non-silylated cephalosporin compound (V) or the silylated analogue can be used, because of the ease of reaction and the quality of the product obtained the silylated cephalosporin compound is the preferred one for reaction with compound (I) in forming the amide bond at the 7-position.

Compound (VIII) can be isolated from the reaction mixture by water and extraction of the product into a suitable organic solvent. The compound (VIII) can thereafter be isolated by evaporation of the solvent and optional crystallization of the residue thus obtained.

Alternatively, the compound of formula (VIII) need not be isolated and a solution of the same in an organic solvent can be used as such for reaction with thiourea to produce the cephalosporin antibiotics of formula (II).

In Step-B of the process, the compound of formula (II), either isolated or non-isolated, preferably the latter is reacted with thiourea in an organic solvent, optionally containing water and in the presence of a base at low to ambient temperature to effect formation of the aminothiazole ring and thereby, affording the cephalosporin antibiotic compounds of formula (II).

In a typical embodiment, a solution of the intermediate compound of formula (VIII) in a suitable organic solvent is treated with a solution of a mixture of thiourea and a base in water at low to ambient temperature for 2 to 3 hours at a pH between 5.0 to 6.0 to effect cyclisation of the aminothiazole ring and thereby, produce compounds of formula (II).

Any organic solvent can be used in the reaction for formation of compounds of formula (II). However, the formation of compound (II) is best carried out in chlorinated solvents selected from dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons selected from benzene and toluene; nitrile solvents selected from acetonitrile, propionitrile and butyronitrile;

and ether solvents selected from tetrahydrofuran and dioxane. However, chlorinated hydrocarbons and ethers are more preferred and among these dichloromethane and tetrahydrofuran are the preferred solvents.

The base used in the reaction can be an organic or inorganic base, the latter being more preferred since it leads to minimum degradation of the cephalosporin ring. Alkali metal carbonate, such as sodium carbonate, potassium carbonate and lithium carbonate.; alkali metal hydrogen carbonates, such as sodium hydrogen carbonate and potassium carbonate; and alkali metal acetates, such as sodium acetate and potassium acetate can be used as bases.

The reaction is carried out at temperatures ranging from -5^0 C to 40^0 C, preferably between -10^0 C to 30^0 C.

At the end of the reaction the aqueous phase is separated from the organic phase and the compounds of formula (II) are isolated by standard methods known in cephalosporin chemistry.

In the cephalosporin antibiotic compounds of formula (II),
R is hydrogen, C $_{1-4}$ alkyl group, an easily removable hydroxyl protective group,
$-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$, wherein
R_5 is hydrogen, or an easily hydrolysable ester group;
R_1 is hydrogen or $-OCH_3$;
R_2 is hydrogen;
R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester or an alkali or alkaline earth metal;
R_4 is hydrogen or is a substituent useful in cephalosporin chemistry.

The group R_4, which is a substituent useful in cephalosporin chemistry includes *inter alia* those substituents which are conventional in cephalosporin chemistry and which are useful in pharmaceutically active cephalosporins and thus include unsubstituted and substituted alkyl; unsubstituted and substituted alkenyl; alkyl an alkenyl substituted by alkoxy, heterocyclthio, heterocycylcarbonylthio, alkylcarbonyloxy and heterocycyl. Heterocycyl includes 5 or 6

membered heterocycyl including a bicyclic ring system having 10 to 12 carbon atoms; a heterocycyl having 1 to 4 hetero atoms, selected from N, O or S;

When R_3 is a negative charge, the group R_4 may contain a positive charge; e.g. in the form of a positively charged amine.

If R_3 together with the COO^- group to which it is attached is an ester group R_3 preferably forms with the COO^- group a physiologically hydrolysable and acceptable ester, e.g. R_3 is a substituent useful in cephalosporin chemistry.

The term, "easily hydrolysable esters of the compounds of formula (II)" is to be understood as compounds of the formula (II) in which the carboxyl group to which the group R_3 or R_5 is attached is present in the form of an ester group which can be easily hydrolysed. Examples of such esters, which can be of the conventional type, are the lower alkyl esters such as methyl, ethyl, tertiary butyl; alkanoyloxyalkyl esters, e.g. the acetoxy methyl, pivaloxymethyl, 1-acetoxyethyl, 1-pivaloxyethyl ester; the lower alkoxycarbonyloxyalkyl esters, e.g. the methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxyethyl ester; the alkoxymethyl esters, e.g. methoxy methyl ester, and the lower alkylaminomethyl esters, e.g. the acetamidomethyl esters. Other esters, e.g. the benzyl and cyanomethyl esters can also be used.

The term, "an easily removable hydroxyl protective group" is to be understood as compounds of formula (II) in which the group R attached to the oxygen moiety of the oxyimino function are those which protect the oxygen function for further reaction with compound of formula (VII) during the preparation of compound of formula (I) and which can be conveniently be removed after formation of compounds of formula (II). Examples of such hydroxyl protective groups include those of the conventional types routinely used for protection of hydroxyl groups and include *inter alia* trialkyl silyl ethers; trialkylaryl silyl ethers; trialkyl stannyl ethers; trityl; tetrahydropyranyl; alkyl or aryl sulfonates such as tosyl, mesyl, besyl etc.; boron or aluminium containing two alkyl groups; (un)substituted benzyl etc.

Compounds of formula (II), wherein the group R_3 is hydrogen can be converted into their physiologically acceptable salts or esters by reaction of the carboxylic acid compound with suitable reagents that form the respective salts or esters. For instance, when compound of formula (II) is cefotaxime acid, ceftriaxone acid or ceftiofur acid it can be converted to the corresponding physiologically more active sodium salts by reaction with suitable sodium metal carriers. Similarly, when compound of formula (II) is cefpodoxime acid or cefditoren acid these can be converted into their respective physiologically more active esters like cefpodoxime proxetil and cefditoren pivoxil by reaction with the respective ester forming reagents.

Similarly, compounds of formula (II) in which the group R is an easily removable hydroxyl protective group can be converted to compounds of formula (II) in which R is hydrogen by removal of the protective groups by conventional means. For instance, cefdinir, in which the group R is hydrogen can be obtained by removal of any of the abovementioned hydroxyl groups.

Compounds of formula (II), wherein the group R attached to the oxime function is a group of R_5, such groups can be hydrolysed to a group, wherein R is hydrogen . For instance, cefixime and ceftazidime can be obtained by hydrolysis of the group R_5, which is tertiary butyl or the like in compounds of formula (II).

Alternatively, compounds of formula (II), wherein the group R_3 is an ester group can be converted to compounds wherein R_3 is hydrogen by removal of the ester function.

Further, the compounds of formula (II) may also be obtained as physiologically active solvates or hydrates.

It is to be understood all the abovementioned variations of the process form an embodiment of the present invention.

The commercially valuable cephalosporin compounds of formula (II) that can be manufactured by the process of this invention include, to name a few :

1) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefdinir,

2) 7-[(Z)-2-(2-amino-4-thiazolyl)-2-methoxyimino)acetyl]amino-3-[(1Z)-2-(4-methyl-5-thiazolyl)ethenyl -3-cephem-4-carboxylic acid, i.e. cefditoren and the pivaloyloxymethyl ester i. e. cefditoren pivoxil,

3) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1- methylpyrrolodino) methyl-3-cephem-4-carboxylate i.e. cefepime,

4) 7-[(Z)-2-(2-aminothiazol-4-yl)methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid i.e. cefetamet, and the pivaloyloxymethyl ester i. e. cefetamet pivoxil,

5) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefixime,

6) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-methyl–1H-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefmenoxime,

7) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[[5- carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl]- 3-cephem-4-carboxylic acid i.e. cefodizime,

8) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]- 3-cephem-4-carboxylic acid i. e. cefoselis,

9) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid i.e. cefotaxime,

10) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[92,3-cyclopenteno-1-pyridinium)methyl]- 3-cephem-4-carboxylic acid i.e. cefpirome,

11) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate- i.e. cefpodoxime and the 1-methylethoxycarbonyloxy ether i. e. cefpodoxime proxetil,

12) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-5,6,7-tetrahydroquinolinium-4-carboxylic acid inner salt i. e. cefquinome,

13) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethyl)oximinoacetamido}-3-[pyridinium]methyl-3-cephem-4-carboxylacid acid inner salt i. e. ceftazidime,

14) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(5-methyl-1,2,3,4-tetrazoyl)-methyl-3- cephem-4-carboxylic acid i. e. cefteram and the and the pivaloyloxymethyl ester i. e. cefteram pivoxil,

15) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid i. e. ceftiofur,

16) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid i. e. ceftizoxime,

17) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid i. e. ceftriaxone, and

18) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-ylthio)methyl]- 3-cephem-4-carboxylic acid i. e. cefuzonam.

The invention can be further illustrated by the following examples, which should not be construed as limiting the scope and spirit of the invention.

Example-1

General method for Preparation of 4-halo-2-oxyimino-3-oxo butyric acid- N, N-dimethyl formiminium chloride chlorosulfate of formula (I)

N, N-dimethyl formamide (1.0 mole) is added to a mixture of sulfuryl chloride (1 mole) and of methylene chloride slowly over 30 mins, at a temperature of –20 to –10 ^{0}C. The mixture is stirred for 2 hrs at 20-22 ^{0}C. Further methylene chloride is added and the mixture is allowed to settle down. N, N-dimethyl formiminium chloride chlorosulfate (DFCCS, VII) that remains in the denser organic layer is separated.

The solution of DFCCS (VII) in methylene chloride is added to a solution of containing0.75 moles of 4-halo-2-oxyimino-3-oxo- butyric acid of formula (IV^1) in methylene chloride over 30 min at –25 to –15 ^{0}C.The reaction mixture was stirred for two hours at 5-10 ^{0}C to give the title compound (I). i. e. 4-halo-2-oxyimino-3-oxo butyric acid- N, Ndimethyl formiminium chloride chlorosulfate of formula (I)

Example-2

Preparation of 4-bromo-2(Z)-methoxyimino-3-oxo butyric acid- N, N-dimethyl formiminium chloride chlorosulfate of formula (I)

26.6 g (0.364 moles) of dimethyl formamide was added to a mixture of 49.12 g (0.363 moles) of sulfuryl chloride and 50 ml of methylene chloride slowly over 30 mins, at a temperature of –20 to –10 ^{0}C. The mixture was stirred for 2 hrs at 20-22 ^{0}C. Further 200 ml of methylene chloride was added and the mixture was allowed to settle down. N, N-dimethyl formiminium chloride chlorosulfate (DFCCS, VII) that remains in the denser organic layer was separated.

The solution of DFCCS (VII) in methylene chloride was added to a solution of 63.39 g (0.283 moles) of 4-bromo-2 (Z)-methoxyimino-3-oxo- butyric acid (IV^1) in 800 ml of methylene chloride over 30 min at –25 to –15 ^{0}C.The reaction mixture was stirred for two hours at 5-10 ^{0}C. to give the title compound (I) i. e. 4-bromo-2-methoxyimino-3-oxo butyric acid- N, N-dimethyl formiminium chloride chlorosulfate of formula (I)

^{1}HNMR (DMSO-d_6): δ, 13.4 (s, 1H), 8.2 (s, 1H), 4.3 (s, -$BrCH_2$), 4.1 (s, -OCH_3), 3.2 and 3.1 (-N $(CH_3)_2$.

IR (main bands) in cm^{-1}: 1784

Mass Spectrum : m/z 397.5 amu in the +APCI ionization mode.

Example-3

Preparation of Sodium salt of 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid (cefotaxime sodium)

Step A : Preparation of 4-bromo-2-methoxyimino-3-oxo butyric acid- N, N-dimethyl formiminium chloride chlorosulfate of formula (I)

The title compound was prepared as described in Example-2.

Step B : Preparation of silylated 7-amino cephalosporanic acid :

81.0 g (0.297 moles) of 7-amino cephalosporanic acid (7-ACA) and 72.3 g (0.448 moles) of hexamethyl disilazane (HMDS) were taken in 600 ml of methylene chloride and were refluxed for 3-4 hrs. to give the silylated 7-amino cephalosporanic acid.

Step C: Preparation of 7-[4-bromo-2(Z)-methoxyimino-3-oxobutyramido]- cephalosporanic acid

The solution of silylated 7-ACA in methylene chloride obtained from Step B was added to the solution of 4-bromo-2-methoxyimino-3-oxo butyric acid- N, N-dimethyl formiminium chloride chlorosulfate in methylene chloride obtained from Step A over a period of 30 mins, at a temperature maintained between –80 to –50 ^{0}C. To the mixture was added 54 g (0.446 moles) of dimethylaniline and the progress of the reaction was monitored by HPLC and after

completion of reaction gives the title compound i. e. 7-[4-bromo-2 (Z)-methoxyimino-3-oxobutyramido]- cephalosporanic acid.

^{1}H NMR (DMSO-d_6): δ, 9.43 (1H,d, NHCO), 5.80 (1H,dd, H-7), 5.14 (1H,d, H-6), 5.03, 4.61 (1H each, d, 3-CH_2OCOCH_3), 4.64 (2H,s, $BrCH_2$-), 4.06 (3H, s, -OCH_3), 3.64 (2H, ABq, SCH_2-), 2.02 (3H,s, $OCOCH_3$)

Step D : Preparation of cefotaxime

27.2 g (0.3579 moles) of thiourea and 48.6 g (0.3573 moles) of sodium acetate tri hydrate was dissolved in 250 ml of water. This mixture was added to a mixture containing the solution of 7-[4-bromo-2 (Z)-methoxyimino-3-oxobutyramido]-cephalosporanic acid in methylene chloride, as obtained in Step C and 490 ml of water over 30 mins. The reaction mixture was stirred for 2-3 hrs. The pH of the solution was adjusted to 5.5 with aqueous sodium bicarbonate.

The aqueous layer was separated and treated with activated carbon and filtered. To the filtrate 440 ml of tetrahydrofuran (THF) was added and the pH of the mixture was gradually adjusted to 2.8 with hydrochloric acid. The white solid obtained was filtered and dried at 45 ^{0}C for 4 hrs under vacuum to give 65.6 g (40.3% yield) of 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid (cefotaxime)

Step E : Preparation of cefotaxime sodium

20 g (0.0438 moles) of cefotaxime (from Step D) was dissolved in a mixture of 40 ml methanol and 20 ml ethyl acetate using triethylamine. To the solution was added a solution of 8.4 g (0.0506 moles) of 2-ethyl sodium hexanoate, followed by 250 ml of ethyl acetate. The precipitated white solid was filtered and dried at 45 ^{0}C under vacuum to give 18.6 g (88.7% yield) of the sodium salt of 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid (cefotaxime sodium) having a purity of 99.0%.

Example –4

Preparation of disodium salt of 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid (ceftriaxone sodium)

Step A : Preparation of 4-bromo-2-methoxyimino-3-oxo butyric acid- N, N-dimethyl formiminium chloride chlorosulfate of formula (I)

The title compound was prepared as described in Example-2.

Step B : Preparation of silylated 7-amino-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid

74.0 g (0.458 moles) of hexamethyldisilazane (HMDS) and 10.8 g (0.099 moles) of trimethyl chlorosilane (TMCS) was added to a suspension of the 100 g (0.2695 moles) of 7-amino-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid and 800 ml of methylene chloride and the mixture refluxed was refluxed for 8 hrs to give silylated 7-amino-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid.

Step C : Preparation of 7-[4-bromo-2(Z)-methoxyimino-3-oxobutyramido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid (VIII)

The solution of silylated 7-amino-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid in methylene chloride as obtained in Step B was added to the solution of 4-bromo-2-methoxyimino-3-oxo butyric acid- N, N-dimethyl formiminium chloride chlorosulfate in methylene chloride, as obtained from Step A over a period of 30 min while maintaining the temperature between –80 to –50 ^{0}C. To the mixture was added 42.4 g. (0.350 moles) of dimethylaniline and the progress of the reaction was monitored by HPLC.

After completion of the reaction 800 ml of water and 400 ml of THF were added to the reaction mixture at room temperature and agitated. The organic layer containing 7-[4-bromo-2(Z)-methoxyimino-3-oxobutyramido]-3--[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid was separated and used as such for the next step.

Step D : Preparation of ceftriaxone

24.6 g (0.323 moles) of thiourea and 22.6 g (0.269 moles) of sodium bi carbonate was dissolved in 200 ml of water. This mixture was added to a mixture containing the solution of 7-[4-bromo-2(Z)-methoxyimino-3-oxobutyramido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid in the organic solvent, as obtained from Step C and 600 ml of water over a period of 30 mins. The reaction mixture was stirred for 60 mins at 5-10 ^{0}C. The pH of the solution was adjusted to 5.5 with aqueous sodium bicarbonate solution. The reaction was further stirred for 2-3 hrs..

The aqueous layer was separated and treated with activated carbon and filtered. To the filtrate 360 ml of ethyl acetate and 78 ml of IPA were added and the pH of the mixture was gradually adjusted to 2.8 by addition of formic acid. The precipitated white solid of was filtered and dried at 45 ^{0}C for 4 hrs under vacuum to give 80.4 g (51.25% yield) of 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid (ceftriaxone) having a purity of 90.56%.

Step E : Preparation of ceftriaxone sodium

20 g (0.036 moles) of the ceftriaxone, obtained from from Step D was added to 120 ml water. To this was added triethylamine for complete dissolution of ceftriaxone. The clear solution was treated with activated carbon and filtered. To the filtrate was added 12.85 g (0.0774 moles) of 2-ethyl sodium hexanoate in 800 ml of acetone at 0-5 ^{0}C. The precipitated white solid t was filtered, washed and dried under vacuum at 25 ^{0}C to give 18.5 g (77% yield) of the disodium salt of 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,5-dihydro-6-hydroxy-

2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid (ceftriaxone sodium), having a purity of 94%.

Example –5

Preparation of 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid (ceftiofur)

Step A : Preparation of 4-bromo-2-methoxyimino-3-oxo butyric acid- N, N-dimethyl formiminium chloride chlorosulfate of formula (I)

The title compound was prepared as described in Example-2.

Step B : Preparation of silylated 7-amino-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid

30.4 g (0.1883 moles) of hexamethyldisilazane (HMDS) and 20.32 g (0.1873 moles) of trimethyl chlorosilane (TMCS) were added to the suspension of 80 g (0.2352 moles) of 7-amino-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid in 800 ml of methylene chloride and the mixture was refluxed for 3 hrs for complete silylation to give silylated 7-amino-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid.

Step C :Preparation of 7-[4-bromo-2(Z)-methoxyimino-3-oxobutyramido]-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid

The solution of silylated 7-amino-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid in methylene chloride as obtained in Step B was added to the solution of 4-bromo-2-methoxyimino-3-oxo butyric acid-N, N-dimethyl formiminium chloride chlorosulfate in methylene chloride, as obtained from Step A over a period of 30 min while maintaining the temperature between –25 to –15 ^{0}C. To the mixture was added 38.4 g. (0.173 moles) of dimethylaniline and the progress of the reaction was monitored by HPLC.

After completion of the reaction 800 ml of water was added to the reaction mixture at room temperature and agitated. The organic layer containing 7-[4-bromo-2(Z)-methoxyimino-3-oxobutyramido]-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid was separated and used as such for the next step.

^{1}HNMR (DMSO-d_6): δ, 5.93 (1H,dd, H-7), 5.17 (1H,d, H-6), 4.37 (1H,s,–S-CO-), 4.59 (2H,s, $BrCH_2$-), 4.20 (3H, s, $-OCH_3$), 3.78 (2H,s, SCH_2-).

IR (main bands) in cm^{-1}: 1780

Step D : Preparation of ceftiofur

25.0 g (0.3289 moles) of thiourea was dissolved in 160 ml of demineralised water. This solution was added to a mixture containing 7-[4-bromo-2(Z)-methoxyimino-3-oxobutyramido]-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid in methylene chloride, as obtained from Step C 240 ml of tetrahydrofuran (THF) over a period of 30 mins. The reaction mixture was stirred for 2 hrs at 5-10 ^{0}C. The pH of the solution was adjusted to 5.0 with aqueous sodium bicarbonate solution.

The aqueous layer was separated and the pH of the mixture was gradually adjusted to 3.0. The white solid precipitated was filtered and dried at 45 ^{0}C for 3 hrs under vacuum to give 1.65 g (21.4% yield) of 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid (ceftiofur)

Example-6

Following the methods described in Examples 1-5 the following cephalosprorin compounds of formula (II) were prepared by utilizing the requisite starting compounds (I) and (VII). The compounds are :

i) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefdinir,

ii) 7-[(Z)-2-(2-amino-4-thiazolyl)-2-methoxyimino)acetyl]amino-3-[(1Z)-2-(4-methyl-5-thiazolyl)ethenyl -3-cephem-4-carboxylic acid, i.e. cefditoren and the pivaloyloxymethyl ester i. e. cefditoren pivoxil,

iii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1- methylpyrrolodino) methyl-3-cephem-4-carboxylate i.e. cefepime,

iv) 7-[(Z)-2-(2-aminothiazol-4-yl)methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid i.e. cefetamet, and the pivaloyloxymethyl ester i. e. cefetamet pivoxil,

v) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefixime,

vi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-methyl--1H-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefmenoxime,

vii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[[5- carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl]- 3-cephem-4-carboxylic acid i.e. cefodizime,

viii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]- 3-cephem-4-carboxylic acid i. e. cefoselis,

ix) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[92,3-cyclopenteno-1-pyridinium)methyl]- 3-cephem-4-carboxylic acid i.e. cefpirome,

x) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate- i.e. cefpodoxime and the 1-methylethoxycarbonyloxy ether i. e. cefpodoxime proxetil,

xi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-5,6,7-tetrahydroquinolinium-4-carboxylic acid inner salt i. e. cefquinome,

xii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethyl)oximinoacetamido}-3-[pyridinium]methyl-3-cephem-4-carboxylacid acid inner salt i. e. ceftazidime,

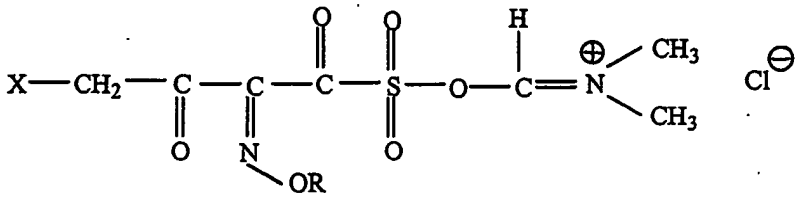
xiii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(5-methyl-1,2,3,4-tetrazoyl)-methyl-3- cephem-4-carboxylic acid i. e. cefteram and the and the pivaloyloxymethyl ester i. e. cefteram pivoxil,

xiv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid i. e. ceftizoxime, and

xv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-ylthio)methyl]- 3-cephem-4-carboxylic acid i. e. cefuzonam.

Claims :

1. A novel 4-halo-2-oxyimino-3-oxo butyric acid-N, N-dimethyl formiminium chloride chlorosulfate of formula (I) useful in the preparation of cephalosporin antibiotics



(I)

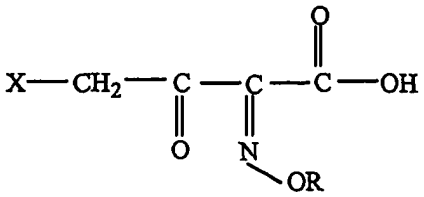
wherein

X is chlorine or bromine;

R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$

wherein R_5 is hydrogen or an easily hydrolysable ester group.

2. A process for preparation of compound of formula (I) comprising reacting 4-halo-2-oxyimino-3-oxobutyric acid of formula (IV^1),



(IV^1)

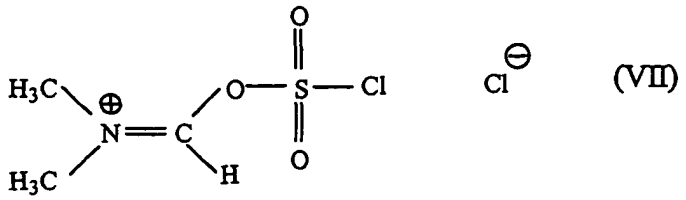
wherein

X is chlorine or bromine;

R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$

wherein R_5 is hydrogen or an easily hydrolysable ester group.

with N, N-dimethylformiminium chloride chlorosulphate of formula (VII)



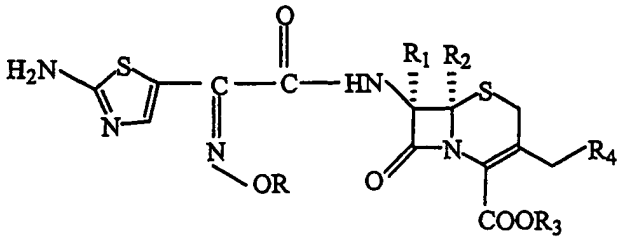
(VII)

in an organic solvent at a temperature ranging from -30^0 C to -15^0 C.

3. A process according to Claim 2, wherein the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, or chloroform; aromatic hydrocarbons such as benzene or toluene; and nitriles such as acetonitrile, propionitrile or butyronitrile.

4. A process according to Claim 2, wherein the molar ratio of compound of formula (VII) to compound of formula (IV^1) is between 1.1 to 1.3.

5. A process for preparation of a cephalosporin compound of formula (II),



(II)

wherein

R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, -CH_2COOR_5, or -$C(CH_3)_2COOR_5$

wherein R_5 is hydrogen or an easily hydrolysable ester group.

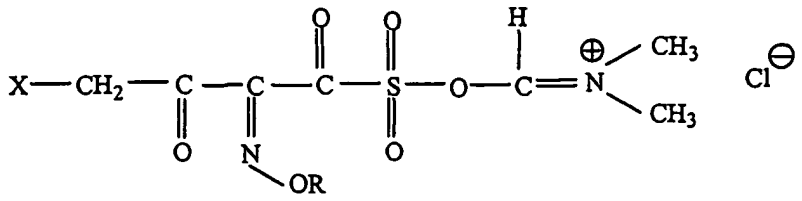
R_1 is hydrogen or $-OCH_3$;

R_2 is hydrogen;

R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal,

R_4 is hydrogen or is a substituent useful in cephalosporin chemistry;

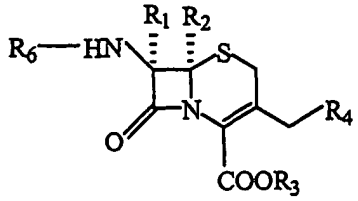
comprising reaction of compound of formula (I)



(I)

wherein X is chlorine or bromine; R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$, wherein R_5 is hydrogen or an easily hydrolysable ester group

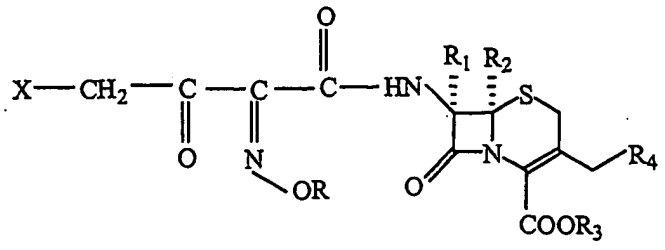
with 7-amino cephalosporanic acid of formula (V),



(V)

wherein R_1 is hydrogen or $-OCH_3$; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal, or is a silyl group; R_4 is hydrogen or is a substituent useful in cephalosporin chemistry; R_6 is hydrogen or a silyl group with the proviso that, when R_3 is hydrogen R_6 is also hydrogen; when R_3 is a silyl group R_6 is also a silyl group; and when R_3 is an ester, or an alkali or alkaline earth metal R_6 is hydrogen

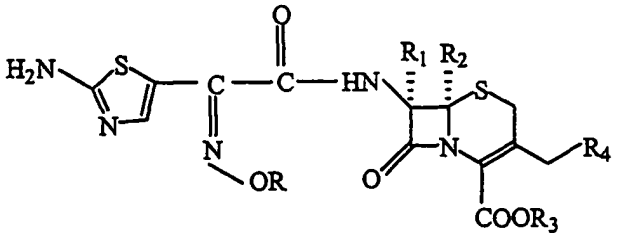
to give 7-[(4-halo-2-oxyimino-3-oxobutyramido-3-substituted-3-cephem-4-carboxylic acid of formula (VIII),



(VIII)

wherein X, R, R_1, R_2 and R_4 have the same meanings as defined hereinearlier, and R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal.

followed by cyclisation of compound (VIII) with thiourea to give compound of formula (II),



(II)

wherein R and R_5 are as defined above; R_1 is hydrogen or $-OCH_3$; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester or an alkali or alkaline earth metal; R_4 is hydrogen or is a substituent useful in cephalosporin chemistry.

6. A process according to Claim 5, wherein the reaction of compound (I) and compound (V) to give compound (VIII) is carried out in an organic solvent and in the presence of a base at a temperature ranging from -80^0 C to -15^0 C,.

7. A process according to Claims 5 or 6, wherein the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons such as benzene and toluene; nitrile solvents such as acetonitrile, propionitrile and butyronitrile; ethers such as tetrahydrofuran and dioxane.

8. A process according to Claims 5 or 6, wherein the base is selected from N, N dimethyl aniline, diethyl amine, and pyridine.

9. A process according to Claims 5 or 6, wherein the molar ratio of compound (I) to the cephalosporin compound (V) is between 1.1 to 2.0, preferably between 1.2 to 1.5.

10. A process according to Claims 5 or 6, wherein the preferred temperature is between –55^0 C to –25^0 C.

11. A process according to Claim 5, wherein the reaction of compound (VIII) and thiourea to give the cephalosporin compounds of formula (II) is carried out in a mixture of organic solvent and water and in the presence of a base at low to ambient temperature.

12. A process according to Claims 5 or 11, wherein the the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons such as benzene and toluene; nitrile solvents such as acetonitrile, propionitrile and butyronitrile; ethers such as tetrahydrofuran and dioxane.

13. A process to Claims 5 or 11, wherein the base is selected from alkali metal carbonates, such as sodium carbonate, potassium carbonate and lithium carbonate; alkali metal hydrogen carbonates, such as sodium hydrogen carbonate and potassium carbonate; and alkali metal acetates, such as sodium acetate and potassium acetate.

14. A process according to Claims 5 or 11, wherein the temperature is between –5^0 C to 40^0 C, preferably between –10^0 C to 30^0 C.

15. A process according to Claim 5, wherein the compound of formula (II) is any one of

i) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefdinir,

ii) 7-[(Z)-2-(2-amino-4-thiazolyl)-2-methoxyimino)acetyl]amino-3-[(1Z)-2-(4-methyl-5-thiazolyl)ethenyl -3-cephem-4-carboxylic acid, i.e. cefditoren and the pivaloyloxymethyl ester i. e. cefditoren pivoxil,

iii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methylpyrrrolodino) methyl-3-cephem-4-carboxylate i.e. cefepime,

iv) 7-[(Z)-2-(2-aminothiazol-4-yl)methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid i.e. cefetamet, and the pivaloyloxymethyl ester i. e. cefetamet pivoxil,

v) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefixime,

vi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-methyl–1H-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefmenoxime,

vii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[[5-carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl]- 3-cephem-4-carboxylic acid i.e. cefodizime,

viii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]- 3-cephem-4-carboxylic acid i. e. cefoselis,

ix) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid i.e. cefotaxime,

x) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[92,3-cyclopenteno-1-pyridinium)methyl]- 3-cephem-4-carboxylic acid i.e. cefpirome,

xi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate- i.e. cefpodoxime and the 1-methylethoxycarbonyloxy ether i. e. cefpodoxime proxetil,

xii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-5,6,7-tetrahydroquinolinium-4-carboxylic acid inner salt i. e. cefquinome,

xiii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethyl)oximinoacetamido}-3-[pyridinium]methyl-3-cephem-4-carboxylacid acid inner salt i. e. ceftazidime,

xiv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(5-methyl-1,2,3,4-tetrazoyl)-methyl-3- cephem-4-carboxylic acid i. e. cefteram and the and the pivaloyloxymethyl ester i. e. cefteram pivoxil,

xv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid i. e. ceftiofur,

xvi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid i. e. ceftizoxime,

xvii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid i. e. ceftriaxone, and

xviii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-ylthio)methyl]- 3-cephem-4-carboxylic acid i. e. cefuzonam.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/IN 02/00245

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C305/00 C07C303/24 C07D501/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 458 949 B1 (V.K. HANDA, ET AL.) 1 October 2002 (2002-10-01) cited in the application column 3, line 55 - column 4, line 34; claim 1	1-15
Y	EP 0 791 597 A (LUPIN LABORATORIES) 27 August 1997 (1997-08-27) cited in the application page 9, line 11 - line 56 page 17; claims 1-5,9,14; examples	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2003	10/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Int. ional Application No
PCT/IN 02/00245

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6458949 B1	07-03-2002	US 2002028931 A1	07-03-2002
EP 0791597 A	27-08-1997	EP 0791596 A1	27-08-1997
		EP 0791597 A1	27-08-1997
		DE 69702463 D1	17-08-2000
		DE 69702463 T2	22-03-2001

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 October 2004 (28.10.2004)

PCT

(10) International Publication Number
WO 2004/092183 A2

(51) International Patent Classification[7]: C07D 501/06, 501/44

(21) International Application Number: PCT/EP2004/003988

(22) International Filing Date: 15 April 2004 (15.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

A 586/2003	16 April 2003 (16.04.2003)	AT
A 585/2003	16 April 2003 (16.04.2003)	AT
A 584/2003	16 April 2003 (16.04.2003)	AT

(71) Applicant *(for all designated States except US)*: **SANDOZ AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LUDESCHER, Johannes** [AT/AT]; Kleinsöll 101, A-6252 Breitenbach (AT). **STURM, Hubert** [AT/AT]; Edith-Stein-Weg 2, A-6020 Innsbruck (AT). **WOLF, Siegfried** [AT/AT]; Judenwiese 4a, A-6230 Brixlegg (AT).

(74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

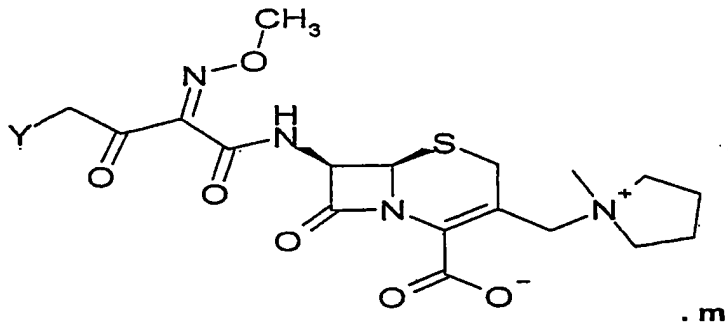
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CEFEPIME PROCESSES



(V)

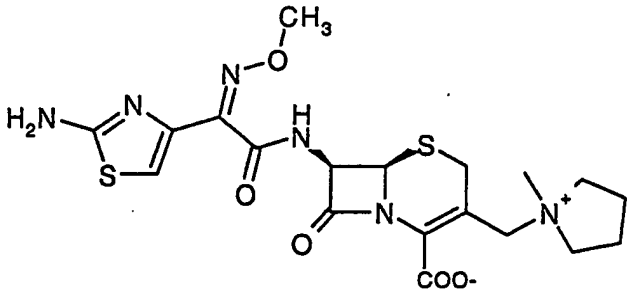
. m HX

(57) Abstract: This invention provides processes for preparing cefepime, including crystalline intermediates.

WO 2004/092183 A2

Cefepime processes

The present invention relates to the preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate), hereafter "cefepime". Cefepime is a valuable 4th generation injectable cephalosporin with antibacterial properties, see e.g. The Merck Index Thirteenth Edition, Item 1935, and is used e.g. in the form of a dihydrochloride hydrate of formula I

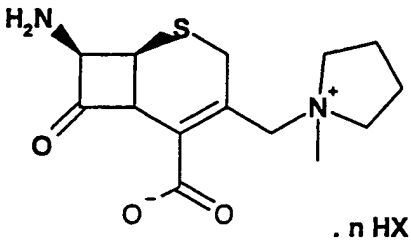


. 2 HCl . H_2O I

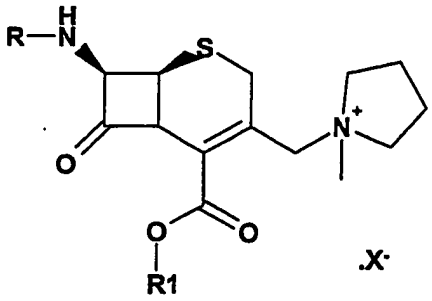
Presently known methods for preparing cefepime are far from straightforward. For example, it is known that the 7-acyl side chain as the difficultly obtainable 2-(2-aminothiazol-4-yl)-2-methoxyimino-acetic acid chloride hydrochloride must be used for the production of cefepime, in order to obtain an active ingredient which is pure in respect of the by-products known as anti-isomer and Δ-2 isomer.

The present applicants have sought to overcome the problems of hitherto known processes.

In one aspect, therefore, this invention provides a process comprising reaction of a β-lactam intermediate of formula IIA or IIB



II A



II B

wherein

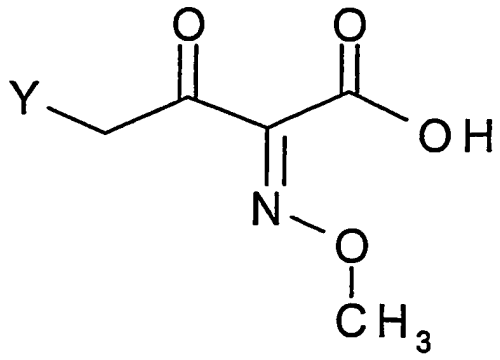
R_1 is trialkylsilyl,

R is H or trialkylsilyl

n is 0 - 2 and

X is chloride, bromide or iodide,

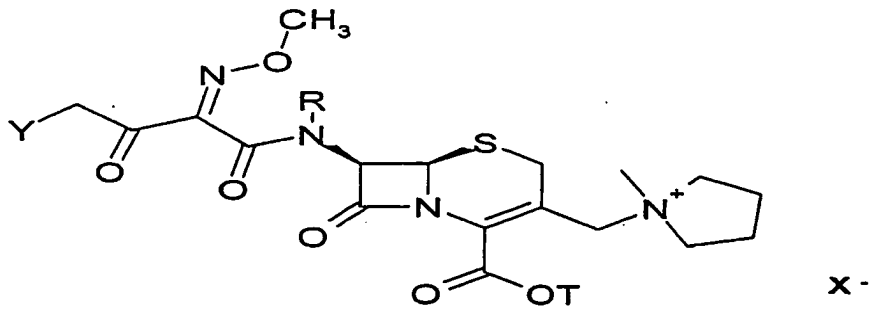
with a reactive derivative of the compound of formula III



III

wherein Y is halogen or a leaving group,

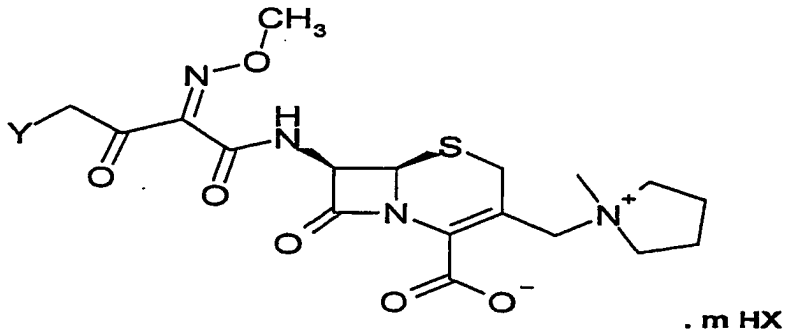
to form a compound of formula IV or V



IV

wherein T is trialkylsilyl, the silyl protecting groups - if present - are removed,

if necessary the intermediate step of formula V



V

is isolated wherein m is 0 or 1,

the compound of formula IV, or the compound of formula V, is reacted with thiourea and subsequently the compound of formula I is isolated.

Examples of trialkylsilyl protecting groups are trimethylsilyl and triethylsilyl.

When Y represents halogen, Y may denote chloride, bromide or iodide, preferably chloride or bromide. Leaving group is understood in the context of this invention to denote a group

which is removed by reaction with e.g. thiourea, e.g. alkyl or aryl sulfonyl, e.g. $C_1 - C_4$ alkyl sulfonyl.

Unless otherwise stated, alkyl means $C_1 - C_8$ alkyl, e.g. $C_1 - C_4$ alkyl, e.g. methyl, ethyl, propyl or butyl and may be straight or branched chain.

Unless otherwise stated, the compounds of formula IIA and IIB are referred to as compounds of formula II.

It will be appreciated that the compounds of formula II or V may exist in mixtures. Thus the compound of formula IIA may exist in a mixture having a proportion where n is 1, and a proportion where n is 2. The compound of formula IIB may exist in a mixture comprising mono- and di-silylated forms.

The compounds of formula II may be used in free base form, as a mono-addition salt or as a di-addition salt with a hydrohalic acid such as hydrochloric acid, hydrobromic acid or hydriodic acid. The addition salts may additionally be present in solvated form, e.g. as a hydrate.

If the silylation variant is chosen, the intermediate of formula IIB is obtained by known methods, using a silylation agent such as N,O-bis-(trimethylsilyl)-acetamide (BSA), N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA), N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA) or for example hexamethyldisilazane (HMDS), in a solvent that is inert towards silylation agents, for example a nitrile, such as acetonitrile, an ether, for example tetrahydrofuran, or a chlorinated hydrocarbon, for example dichloromethane.

Subsequently, the silylated derivative of formula IIB is acylated with a reactive derivative of formula III, the reactive derivative being an acid chloride, acid bromide or active ester, for example a S-mercaptobenzothiazolyl ester, optionally in the presence of an auxiliary base such as a tertiary alkylamine.

The compound of formula IV is subsequently desilylated with the assistance of a protic reagent, for example water or an alcohol, and then the compound of formula V is reacted with thiourea in an aqueous or organic-aqueous medium. Cefepime is subsequently crystallised, if necessary after separating the organic solvent, and where appropriate after removing any salt that is present, for example after treatment using anion exchangers by known methods after adding hydrochloric acid from an aqueous acetonic solution.

An alternative is to work in an aqueous or aqueous-organic system, for example in a one-phase system consisting of water and a water-miscible solvent, for example a ketone, such as acetone, a nitrile, such as acetonitrile, or an ether, such as tetrahydrofuran, or in a two-phase system, for example in a combination of an ester of acetic acid, for example ethyl acetate, a chlorinated hydrocarbon, for example dichloromethane, or for example an aromatic hydrocarbon, for example toluene, whereby the compound of formula IIA is optionally released from its respective mono- or di-addition salt form with the assistance of a base, for example caustic soda solution or caustic potash solution, a sodium or potassium hydrogen carbonate or alkali carbonate, or by known methods using an ion exchanger, and subsequently the compounds of formula II are acylated with a reactive derivative of formula III. After the acylation reaction has taken place, thiourea is added, and after optionally separating the organic solvent, the title compound is isolated by known methods by adding acetone from an aqueous/acetonic solution.

Suitable ion exchangers include ion exchange resins comprising e.g. LA2 which is available commercially from the Rohm and Haas company.

If desired, it is possible to isolate the compound of formula V, at this stage as an addition salt with a hydrohalic acid, for example as the hydrochloride, or isolate as free base. Here, the reaction sequence preferably starts with an acid addition salt of the compound of formula II, via the silylation route. By adding small amounts of protic solvent, for example water or an alcohol, to the compound of formula IV, the silyl groups are removed, and the halide present in the system enables direct crystallisation of the compound of formula V to take place. The preferred mono-addition salt is the monohydrochloride in crystalline form. In order to produce

this, the compound of formula IIA is preferably used as the mono- or di-hydrochloride addition salt, and the preferred solvents for crystallisation are acetonitrile in combination with isopropanol.

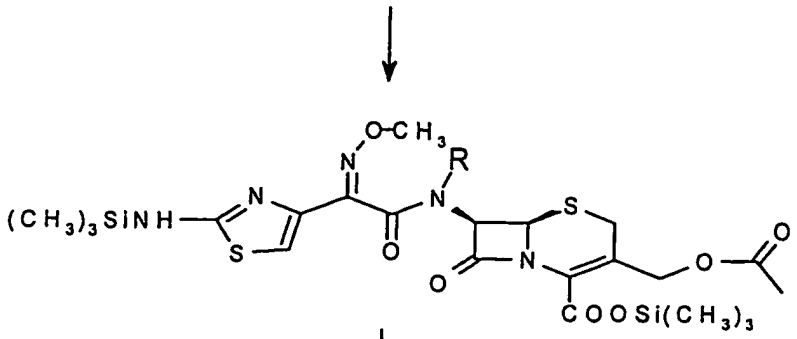
To isolate the compound of formula V as free base in crystalline form, the above procedure may be used with addition of a suitable base to the solution or suspension of the acid addition salt of the compound of formula V. Alternatively, the acid addition salt of the compound of formula V may be isolated and subsequently converted to the corresponding free base by addition of a suitable base. Suitable bases include for example trialkylamines, e.g. triethylamine for example in an alcoholic solvent such as methanol.

In US 4,266,049, a 7-acyl-3-acetoxymethyl-cephalosporinate is converted with the assistance of an iodotrialkylsilane into the corresponding persilylated 3-iodomethyl compound and this then undergoes nucleophilic substitution in the 3'-position. This technology can only be applied to the production of cefepime - starting with cefotaxime - to an uneconomical extent, since N-methylpyrrolidine as a strong base can greatly induce the formation of the by-products Δ-2 und und 7-epi (Walker *et al*, J.Org Chem. 1988, pages 983-991).

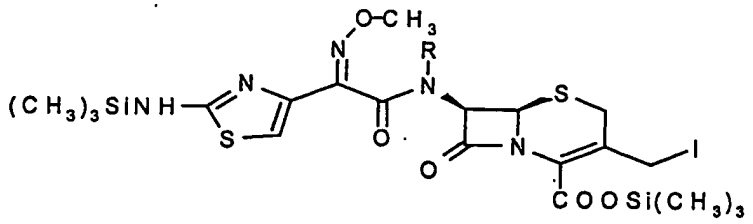
The present applicants found that working with N-methylpyrrolidine - trialkylsilane adducts iodotrimethylsilane and N-methylpyrrolidine as described in the above literature led to unsatisfactory results when using cefotaxime as the starting material.

In another aspect therefore, this invention provides a synthesis route from cefotaxime (see Merck Index, 12th Edition, item 1983) in accordance with the following scheme:

cefotaxime in acid or sodium salt form ->

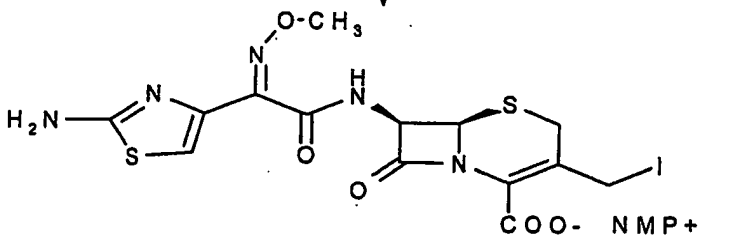


VII

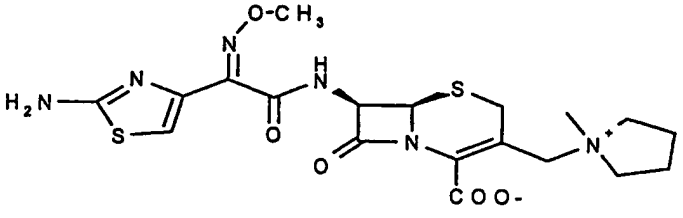


VIII

prot. solvent medium

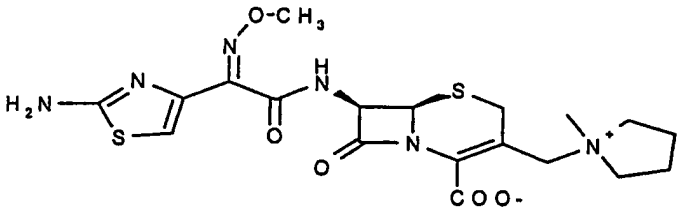


IX



X

. HI



I

. 2HCl . H2O

The choice of silylation agent is crucial to the smooth conversion of cefotaxime into a reactive, silylated derivative of formula VII, whereby R signifies hydrogen or a trialkylsilyl group. Suitable silylation agents are iodotrimethylsilane in the presence of a non-nucleophilic base, N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA), (for example US 4,336,253); N-methyl-N-trimethyl-silyltrifluoroacetamide (MSTFA) (for example EP 74 268); 1,1,1,3,3,3-hexamethyldisilazane (HMDS) or a combination of all the said silylation agents. The compound of formula VIII is then produced in known manner with iodotrimethylsilane.

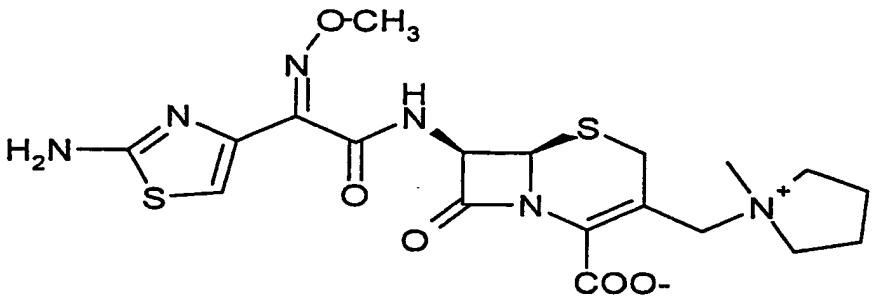
According to the above synthesis method, the silylated compound of formula VIII is treated simultaneously or substantially simultaneously with a protic solvent and N-methylpyrrolidone, whereby in a first step the compound of formula IX is produced and this is then rapidly reacted with N-methylpyrrolidine. The reaction accordingly illustrates a desilylation reaction, followed by salt formation on the carboxylic acid and nucleophilic substitution. This principle simultaneously minimises the instability of the highly reactive iodomethyl grouping by an *in situ* reaction with N-methylpyrrolidine, and through the (desilylation) salt formation on the carboxylic acid, by-product Δ2 formation is drastically reduced.

Suitable protic solvents are, in particular, alcohols, for example C_1-C_4-alcohols, preferred alcohols being ethanol and isopropanol. The amount of protic solvent is not critical, however the applicants have obtained favourable results when the reaction proceeds in a homogeneous solution or suspension, and through insolubility, the compound of formula IX is extracted from the possible further reaction in salt form or in free acid form.

In a preferred embodiment, the compound of formula VIII is mixed with a mixture of N-methylpyrrolidine and alcohol, preferably isopropanol. In this way, not only does the above-described reaction sequence take place, but the title compound is obtained as an addition salt with hydroiodic acid. This can be isolated from the reaction mixture directly. The iodide is removed from the product simply by treatment in an aqueous or aqueous-organic solution, for example in a mixture of dichloromethane/water, with a commercial anion exchanger, for example with Amberlite LA-2 (from Rohm & Haas), and by adding hydrochloric acid the

active ingredient can subsequently be crystallised as the dihydrochloride hydrate according to known methods, for example from an aqueous/acetonic solution.

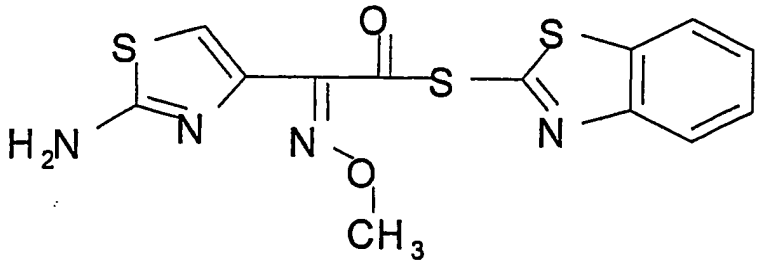
In one embodiment, the isolated hydroiodide may be converted into the corresponding free amphoteric ion (betaine) of formula XI, for example by treatment with a trialkylamine, e.g. trimethylamine, triethylamine or tributylamine, in an organic solvent such as dichloromethane, and after isolation by known methods, this may can be converted into the title compound cefepime dihydrochloride hydrate.



XI

A further aspect of this invention provides a novel process for the production of cefepime which is notable for the simplicity of the choice of solvent and the accessibility and facile handling of the 7-acyl side chain, and which at the same time leads to an active ingredient with high purity in respect of the above-mentioned by-products.

The process comprises the reaction of a pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-halide, an acid addition salt thereof or its free base of formula IIA with (Z)-(2-aminothiazol-4-yl)methoxyimino-acetic acid-2-mercaptobenzothiazolylester of formula XII



XII

in an acetonic or aqueous/acetonic solution, optionally in the presence of a base, wherein cefepime dihydrochloride monohydrate is precipitated in crystalline form directly from the reaction mixture by adding HCl.

The process is straightforward. Neither extraction steps nor more complex purification operations are necessary. The solvent regeneration is an especially simple procedure, in that only one solvent is used both for the acylation reaction and for the crystallisation step. The intermediate compound of formula IIA may be present as mono- addition salt or di-addition salt or a mixture thereof. In addition, the intermediate of formula IIA may be present in the form of a solvate, for example a hydrate. The usual addition salts are represented by the mono- and dihydrochloride or the hydriodide.

Depending on the salt form, the corresponding acid addition salt is released for the reaction with the acylation agent with the assistance of the necessary amount of a base, preferably a trialkylamine. Accordingly, a mono-addition salt is released with approximately one molar equivalent of base, and a di-addition salt is correspondingly released with approximately two. However, it is also possible to react the corresponding acid addition salt with (Z)-(2-aminothiazol-4-yl)methoxyimino-acetic acid-2-mercapto-benzothiazolylester without adding a base.

If the intermediate of formula IIA is used as the mono- or dihydrochloride, the active ingredient cefepime is obtained as the pure dihydrochloride. If the intermediate is used as the hydriodide, the recrystallised product is practically and substantially free from traces of iodide.

Alternatively, foreign ions can be removed from the reaction solutions by known methods, for example with the assistance of an anion exchanger.

Suitable trialkylamines are C_1-C_8-trialkylamines, for example triethylamine or tributylamine. The presence of water in the acylation reaction in principle also allows the use of inorganic bases, for example sodium or potassium hydroxide or an alkali hydrogen carbonate or alkali carbonate, e.g. sodium or potassium hydrogen carbonate or carbonate.

The reaction is preferably carried out in the presence of water: the amount of water is not critical; there must be balanced solubility of the cephalosporin intermediate of formula IIA and of the active ester of formula XII. The water/acetone ratio may be between 1:10 to 10:1, and preferably a water/acetone ratio of 1:1 to 1:5 is used for the acylation reaction. After the acylation reaction, in order to crystallise cefipime dihydrochloride, hydrochloric acid is added, preferably aqueous concentrated hydrochloric acid, and a pH value of less than 3, preferably less than 1, is set. By adding acetone, the crystallisation of cefepime dihydrochloride is then completed. Preferred water/acetone ratios in the crystallisation step are ratios of 1:1 to 1:20, especially ratios of 1:3 to 1:10.

The processes of this invention may be carried out between -40°C and room temperature, for example between -35°C and 15°C, preferably between -25°C and about 1°C.

Following is a description by way of example only of processes of this invention.

Figure 1 is an X-ray spectrum of the compound of formula V as hydrochloride;
Figure 2 is an X-ray spectrum of the compound of formula V as base (betain).

The following abbreviations are used:

NMP^+	to denote N-methylpyrrolidinium
NMP-ACA	to denote an intermediate compound of Formula IIA

Example 1

Preparation of starting material 4-chloro-2-methoxyimino-3-oxo-butyryl chloride

A solution of 0.488 g of 4-chloro-2-methoxyiminobutyric acid in 8.0 ml of acetonitrile is mixed at –20°C with 0.353 g of chloromethylene iminium chloride (Vilsmeier reagent) and stirred for 1 hour at –20°C.

Example 2a

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(4-chloro-2-methoxyimino-3-oxo-butyryl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydrochloride

1.55 g of N,O-bistrimethylsilyacetamide are added dropwise at room temperature to a suspension of 0.835 g of NMP-ACA.2HCl in 10.5 ml of acetonitrile. After stirring for 25 mins at room temperature, the solution obtained is cooled to –35°C. At this temperature, a solution of 4-chloro-2-methoxyimino-3-oxo-butyryl chloride in acetonitrile (for preparation see example 1a), which has been cooled to –20°C, is added. After stirring for 1 hour in a cooling bath at –35°C, 2 ml of isopropanol are added dropwise. The resulting suspension is heated to 0°C and stirred for 1 hour in an ice bath. The suspension is then filtered. The filter cake is washed with acetonitrile. After drying in a vacuum at room temperature, 1.42 g of product is obtained as a white crystalline powder.

^{1}H-NMR spectrum (DMSO-d6, δ in ppm)

1,957 – 1,690 (m, 2H, pyrrolidinyl-H); 2,943 (s, 3 H, N-CH3); 3,371 – 3,701 (m, 5 H, pyrrolidinyl-H, S-CH2); 3,866 (1 H, J = 10,0 Hz, S-CH2); 4,060 (s, 3 H, OCH3); 4,329 and 4,597(ABq, 2 H, J = 13,7 Hz, .-CH2-N); 4,846 (s, 2 H, CH2Cl); 5,322 (d, 1 H, 5,1 Hz, H6); 5,884 (dd, 1H, J = 8,4 Hz, J = 5,1 Hz, H7); 9,555 (d, 1H, NH)

Example 2b

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(4-chloro-2-methoxyimino-3-oxo-butyryl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydrochloride

1.63 g of trimethylsilychloride are added dropwise at room temperature to a suspension of 5.00 g of NMP-ACA.HCl in 190 ml of acetonitrile. After stirring for 10 mins at room temperature 8.5 ml acetontrile are added and then the suspension is cooled to 0°C. At this temperature 7.74 g N,O-bistrimethylsilyacetamide are added dropwise. After stirring for 20 mins the resulting solution is cooled to – 20°C. At this temperatur a solution of 4-chloro-2-methoxyimino-3-oxo-butyryl chloride in acetonitrile (prepared from 3.03 g 4-chloro-2-methoxyimino-3-oxo-butyryl acid, 2.16 g of chloromethylene iminium chloride (Vilsmeier reagent) and 45 ml acetonitrile; preparation see example 1a), which has been cooled to –20°C, is added. After stirring for 1 hour in a cooling bath at –25°C the cold reaction mixture is added within 20 minutes to a mixture of 148 ml acetontrile and 14 ml methanol and by addition of a solution of ethyldiisopropylamine in acetonitrile (10%) the pH is maintained in the range 2.0 – 1.5. The resulting suspension is stirred for 1 hour in an ice bath. The suspension is then filtered. The filter cake is washed with acetonitrile. After drying in a vacuum at room temperature, 7.20 g of product is obtained as a white crystalline powder. The corresponding X-ray spectrum is shown in Figure 1.

Example 2c

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(4-chloro-2-methoxyimino-3-oxo-butyryl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium inner salt

10.64 g of (4-chloro-2-methoxyimino-3-oxo-butyryl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydrochloride (for preparation see above) is suspended in 95 ml cold methanol. To the suspension is added dropwise at 0°C a solution of 8.1g triethylamine in 30 ml methanol. The suspension is stirred for 1 hour in an ice bath. The suspension is then filtered. The filter cake is washed with cold methanol. After drying in a vacuum at room temperature, 7.57 g of product is obtained as a white crystalline powder.

The corresponding X-ray spectrum is shown in Figure 2.

Example 3

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate).

0.990 g of 1-[[(6R,7R)-7-[[(2Z)-(4-chloro-2-methoxyimino-3-oxo-butyryl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydrochloride are added at 4°C to a solution of 0.152 g of thiourea in 5 ml of H_2O. The pH of the suspension is adjusted to pH 6.0 with ion exchanger LA-2 and maintained in the pH range of 5.5 to 6.0 by adding LA-2 dropwise. After stirring for 8.5 hours at 2 to 4°C, the reaction mixture is washed with 10 ml of methylene chloride. After phase separation, the aqueous phase is washed a second time with 10 ml of methylene chloride. The organic phases are combined and then extracted with 3 ml of H_2O. The aqueous phases are combined and mixed with 0.20 g of activated carbon. After stirring for 10 minutes, the carbon suspension is filtered. The carbon cake is washed with 1.5 ml of H_2O. The filtrate and washing water are combined, acidified with 6 m HCl to pH 0.6 and mixed with 50 ml of acetone. After adding seed crystals, stirring is effected for 15 minutes at room temperature, and then a further 50 ml of acetone is added dropwise over the course of 1 hour. The crystal suspension obtained is cooled to 0°C. After stirring for 1 hour in an ice bath, the suspension is filtered and the filter cake is washed with acetone. After drying in a vacuum at room temperature, 0.561 g of the title compound are obtained in the form of a white crystalline powder.

HPLC purity: 99.6 area %

Example 4

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate).

1.55 g of N,O-bistrimethylsilylacetamide are added dropwise at 1°C to a suspension of 0.835 g of pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-

yl)methyl]-dihydrochloride in 10.5 ml of acetonitrile. After stirring for 45 mins in an ice bath, the solution obtained is cooled to –35°C. At this temperature, a solution of 4-chloro-2-methoxyimino-3-oxo-butyryl chloride (for preparation see example 1a), which has been cooled to –20°C, is added. After stirring for 1 hour in a cooling bath at –35°C, 2 ml of H_2O are added dropwise. After stirring for 10 minutes at –35°C, 0.38 g of thiourea are added. The reaction mixture is subsequently heated to 0°C and the pH is adjusted to 6.0 by adding ion exchanger LA-2, and is maintained at this pH. After stirring for 2 hours in an ice bath, the 2-phase reaction mixture obtained is mixed with 2 ml of H_2O. After stirring for a further 16 hours at 0 to 4°C, the pH is acidified to pH 0.6 with 6 m HCl. After adding 50 ml of methylene chloride, the phases are separated. The methylene chloride phase is then extracted with 3 ml of H_2O. The aqueous phases are combined and mixed with 0.10 g of activated carbon. After stirring for 10 minutes, the activated carbon suspension is filtered. The carbon cake is washed with 1 ml of H_2O. The filtrate and washing water are combined and diluted with 30 ml of acetone. After adding seed crystals, stirring is effected for 30 minutes at room temperature. Then, 20 ml of acetone are added dropwise to the resulting crystal suspension over the course of 30 minutes. The suspension is cooled to 0°C. After stirring for 1 hour in an ice bath, the product is isolated and the filter cake is washed with acetone. After drying in a vacuum at room temperature, 0.742 g of the title compound are obtained in the form of a white crystalline powder.

HPLC purity: 99.5 area %

Example 5

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate).

1.706 g of pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-dihydrochloride are added to a mixture of 10 ml of H_2O and 5 ml of methylene chloride, and the pH is adjusted to 6.50 by adding ion exchanger LA-2. The 2-phase mixture is cooled in an ice bath to 1°C. At this temperature, a solution of 4-chloro-2-methoxyimino-3-

oxo-butyryl chloride, produced from 1.464 g of 4-chloro-2-methoxyimino-3-oxo-butyric acid (see example 1a), which has been cooled to –20°C, is added dropwise over the course of 1 hour, whereby the pH is maintained in the range of 6.0 to 6.5 by adding base LA-2. After stirring for 15 minutes in an ice bath, 0.76 g of thiourea are added and stirring is effected for 16 hours at 2-4°C. The pH is maintained in the range of 5.5 to 6.0 with LA-2. The reaction mixture is subsequently diluted with 100 ml of methylene chloride. After phase separation, the aqueous phase is washed with 50 ml of methylene chloride. The methylene chloride phases are combined and then extracted with 3 ml of H_2O. The product-containing aqueous phases are combined and mixed with 0.20 g of activated carbon. After stirring for 10 minutes, the activated carbon suspension is filtered. The carbon cake is washed with 1.5 ml of H_2O. The filtrate and washing water are combined and diluted with 60 ml of acetone. After adding seed crystals, stirring is effected for 30 minutes at room temperature. Then, 40 ml of acetone are added dropwise to the resulting crystal suspension over the course of 30 minutes. The suspension is cooled to 0°C. After stirring for 1 hour in an ice bath, the product is isolated and the filter cake is washed with acetone. After drying in a vacuum at room temperature, 1.236 g of the title compound are obtained in the form of a white crystalline powder.

HPLC purity: 90.0 area %

Example 6

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydriodide

100.0 g of cefotaxime are suspended in 1.2 l of methylene chloride and heated to reflux temperature. Whilst boiling under reflux, 2.5 ml of hexamethyldisilazane (HMDS) and 0.2 ml of trimethyliodosilane are added. Then, 102 ml of HMDS are added dropwise whilst stirring, and stirring is effected at this temperature for 1 hour, whereby the resulting ammonia is removed by passing nitrogen into the reaction suspension. Then, the clear solution obtained is cooled to 10°C. 70 ml of trimethyliodosilane are added dropwise at this temperature. After stirring for 60 minutes, 10 ml of trimethyliodosilane are added dropwise, and after a further 30 minutes, a further 15 ml of trimethyliodosilane are added. After stirring for 165 minutes at

10°C, the reaction solution is stirred over the course of 2 minutes into a solution of 350 ml of N-methylpyrrolidine in 9 l of isopropanol, which has a temperature of 18°C. The resulting suspension is stirred for 1 hour at room temperature. Then, it is filtered through a glass sintering filter and the filter cake is washed with 500 ml of isopropanol. After drying in a vacuum at room temperature, 97.7 g of the title compound are obtained in the form of a yellow coloured powder.

Example 7

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate.

4.00 g of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydriodide are dissolved at room temperature in a mixture of 10 ml of H_2O and 30 ml of methylene chloride. The pH of the mixture is adjusted to 7.3 through the dropwise addition of ion exchanger LA-2. After stirring for 15 minutes, the phases are separated. The aqueous phase is adjusted to pH 2.5 with conc. hydrochloric acid and stirred for 15 minutes. Then, the precipitate formed is separated by filtration. The clear filtrate is acidified to pH 1.0 with conc. hydrochloric acid and mixed with 1.6 g of activated carbon. After stirring for 10 minutes, the activated carbon is removed by filtration and the carbon cake is washed with 5 ml of H_2O. The filtrate and washing water are combined, acidified to pH 0.5 with conc. hydrochloric acid and diluted with 50 ml of acetone. Seed crystals are added, and the resulting crystal suspension is stirred for ca. 20 minutes at room temperature. Subsequently, a further 50 ml of acetone is added dropwise over the course of 30 minutes. When the acetone addition is complete, the crystal suspension is cooled to 0°C. After stirring for 1 hour in an ice bath, the suspension is filtered and the filter cake is washed with acetone. After drying in a vacuum at room temperature, 0.85g of the title compound are obtained in the form of a white crystalline powder. Yield: 36.8%.

HPLC purity: > 99 area %

Example 8

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate

44.3 g of pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-iodide monohydrate (NMP-ACA) are suspended in a mixture of 200 ml of H_2O and 400 ml of acetone. 38.5 g of (Z)-(2-aminothiazol-4-yl)methoxy-iminoacetic acid-2-mercaptobenzothiazolylester are added to the suspension. At a temperature of ca. 15°, a mixture of 13.9 ml of triethylamine and 14 ml of acetone is slowly added dropwiseto the suspension over the course of 3 hours. The resulting cloudy solution is stirred for a total of 6.5 hours at 20°C.

33 ml of 37% HCl are subsequently added to the reaction mixture, and then ca. 300 ml of acetone are added whilst stirring. The mixture is seeded with seed crystals, and within ca. 90 minutes a suspension is produced. Subsequently, within 90 minutes, 1700 ml of acetone are added dropwise whilst stirring gently. The suspension is stirred for a further one hour at room temperature, and then the title compound is isolated through a suction filter, and the product is washed with 250 ml of acetone/H_2O mixture (90/10) and with a total of 500 ml of acetone in two portions. The product is subsequently dried for ca. 18 hours at room temperature in a vacuum drying chamber.

Yield 51.8 g

purity: HPLC: 98.8 area percent

Example 9

Recrystallisation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate

50.0 g of cefepime dihydrochloride hydrate are dissolved in 200 ml of H_2O. 22 ml of 6 n HCl are added and then the solution is mixed with 5 g of activated carbon. The suspension is stirred for 10 minutes at room temperature and then filtered through a suction filter. The filter layer is then washed with 50 ml of H_2O, and the combined filtrates are mixed with 600 ml of acetone until turbidity occurs. The resulting suspension is stirred for 15 minutes and then a further 1400 ml of acetone are added over the course of one hour whilst stirring gently. The suspension is stirred for another one hour at room temperature, and the product is subsequently isolated through a suction filter. The product is washed with a total of 500 ml of acetone and dried for ca. 18 hours at room temperature in a vacuum drying chamber.

Yield 45.01 g

purity HPLC: 99.7 area percent

X-ray diffraction measurements for Examples 2b and 2c

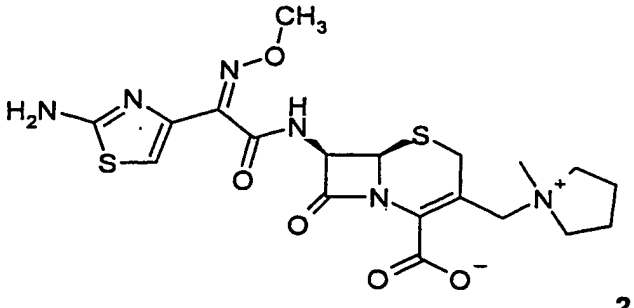
Equipment used:

X-Ray Powder Diffractometer D-8 (AXS-BRUKER)
theta-theta-goniometer, sample changer
target: Copper, Kα1+Kα2 λ = 1.5406 Å
parallel beam optics (receiving soller-slit: 0.07 mm)
Scintillation counter, standard sample holders

Data collection parameters: 40kV, 40 mA, 2-40° θ/2θ, 0.01 steps, 2 seconds

Claims

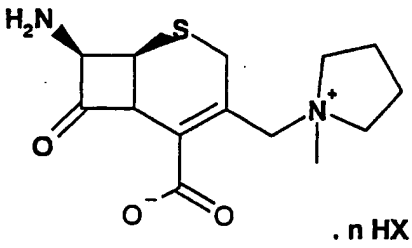
1. A process for producing a compound of formula I



I

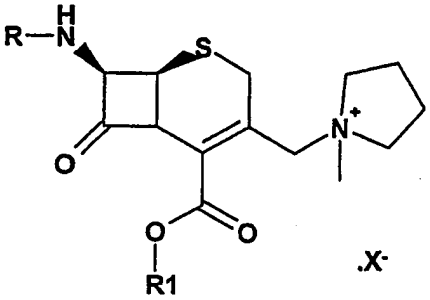
. 2 HCl . H_2O

wherein a compound of formula IIA or IIB



II A

. n HX



II B

.X-

wherein

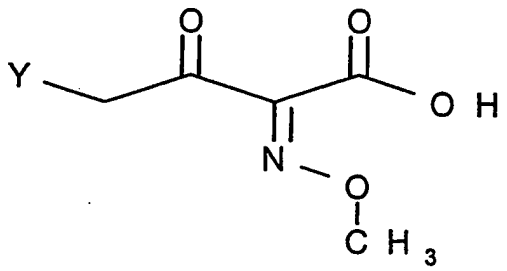
R_1 is a trialkylsilyl group,

R is hydrogen or a trialkylsilyl group,

n is 0 - 2 and

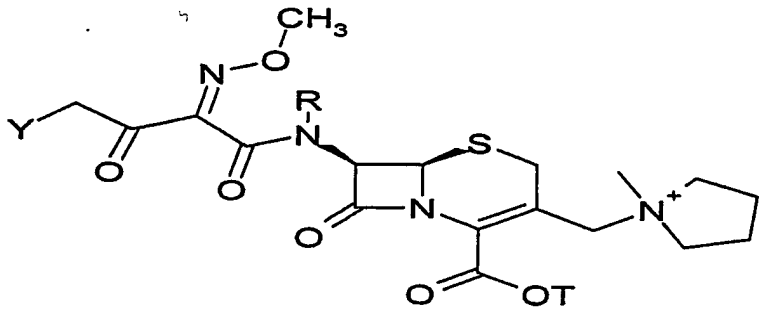
X signifies chloride, bromide or iodide

is reacted with a reactive derivative of formula III



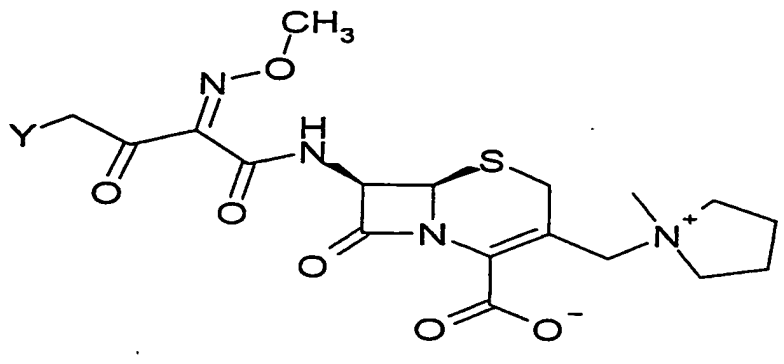
III

wherein Y signifies halogen or a leaving group, to form a compound of formula IV or V



IV

wherein T is trialkylsilyl, the silyl protecting groups, if present, are removed , or the compound of formula IV as the acid addition salt of formula V is isolated wherein m is 0 or 1 and the compound of formula IV



V

. m HX

or the compound of formula V is cyclised with thiourea, and subsequently the compound of formula I is isolated.

2. A process as claimed in claim 1, wherein the compounds of formula II are produced from their respective mono- or di- hydrogen halide adducts.

3. A process as claimed in claim 1 or 2, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-iodide monohydrate is used.

4. A process as claimed in claim 1 or 2, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-chloride or pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-dihydrochloride is used, optionally in solvated form.

5. A compound of formula V, wherein Y and X are Cl.

6. A compound as claimed in claim 5 in crystalline form wherein the compound of formula V is in free base or acid addition salt form.

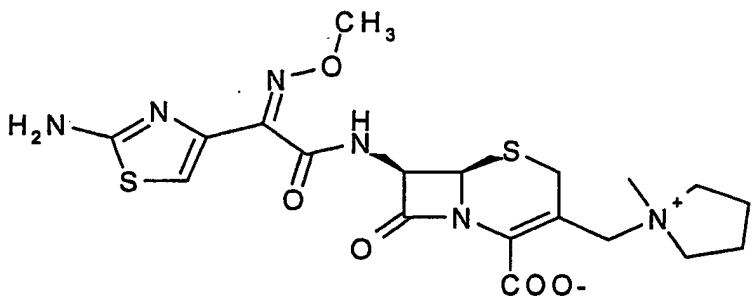
7. A compound as claimed in claim 6 having an X-ray powder diffraction pattern substantially as that shown in Figure 1 or Figure 2.

8. A process according to claim 1, characterised in that 4-chloro-2-methoxyimino-3-oxo-butyryl chloride is used as the reactive derivative of formula III.

9. A process as claimed in any of claims 1 to 5 or 8, wherein prior to precipitation or crystallisation of the compound of formula I, any bromide or iodide ions that may be present are removed by ion exchange.

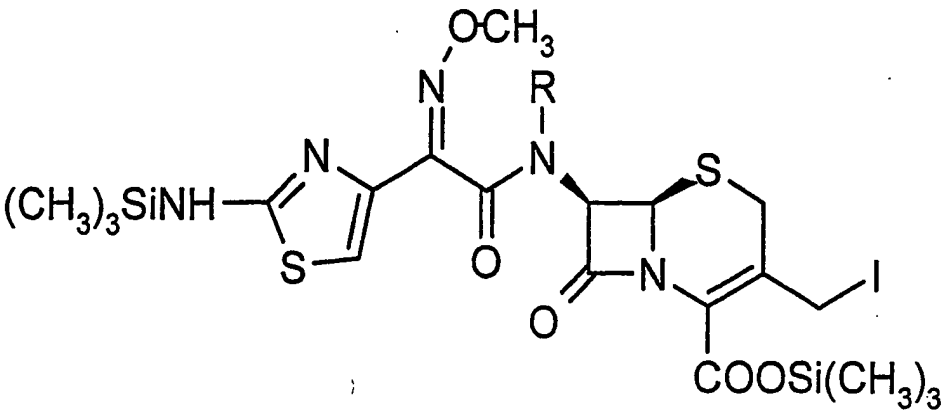
10. A process for producing the compound of formula I

I

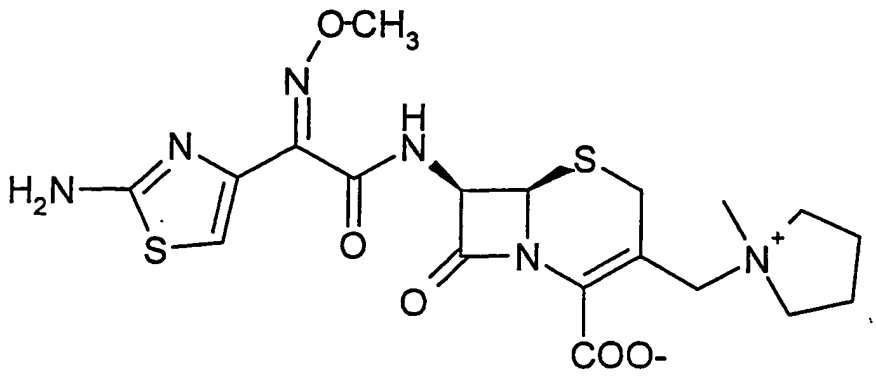


. 2 HCl . H_2O

characterised in that a compound of formula VIII



is desilylated in a protic solvent, and subsequently reacted with N-methylpyrrolidine to form a compound of formula X, and this is then converted into the compound of formula I

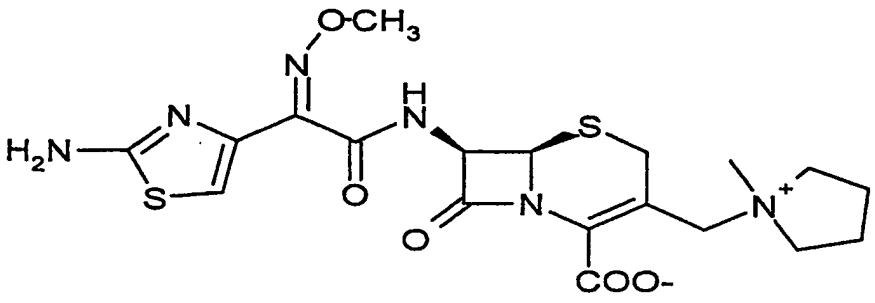


X . HI

11. A process as claimed in claim 10, wherein the protic solvent is a C_1-C_4-alcohol.

12. A process according to claim 10 or 11, wherein conversion of the compound of formula VIII is effected using a basic ion exchanger.

13. A process as claimed in claim 10, 11 or 12, wherein conversion of the compound of formula X into the compound of formula I is effected through the free betaine of formula XI in isolated form

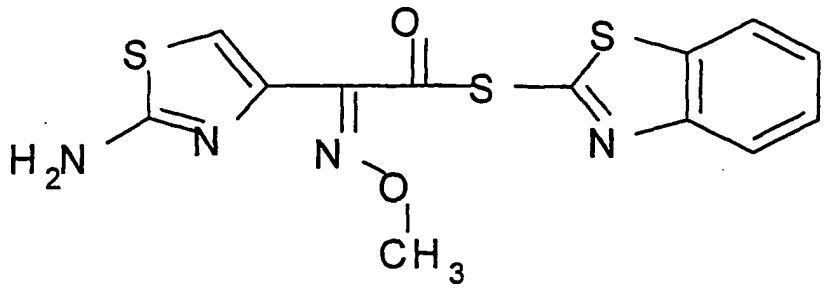


XI .

14. A process for producing the compound of formula I

characterised in that a compound of formula IIA, in unsolvated or solvated form, is reacted optionally after addition of a base, with a compound of formula XII

XII



in acetone or aqueous acetone, and the compound of formula I precipitated in crystalline form from the reaction mixture by adding HCl.

15. A process as claimed in claim 14, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-iodide monohydrate is used.

16. A process as claimed in claim 14, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-chloride is used, optionally in solvated form.

17. A process as claimed in claim 14, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-dihydrochloride is used, optionally in solvated form.

18. A process as claimed in any one of claims 14 to 17, wherein a C_1-C_8-trialkylamine, KOH or NaOH, or an alkali hydrogen carbonate or potassium carbonate, is used as the base.

G-33166 A

FIGURE 1

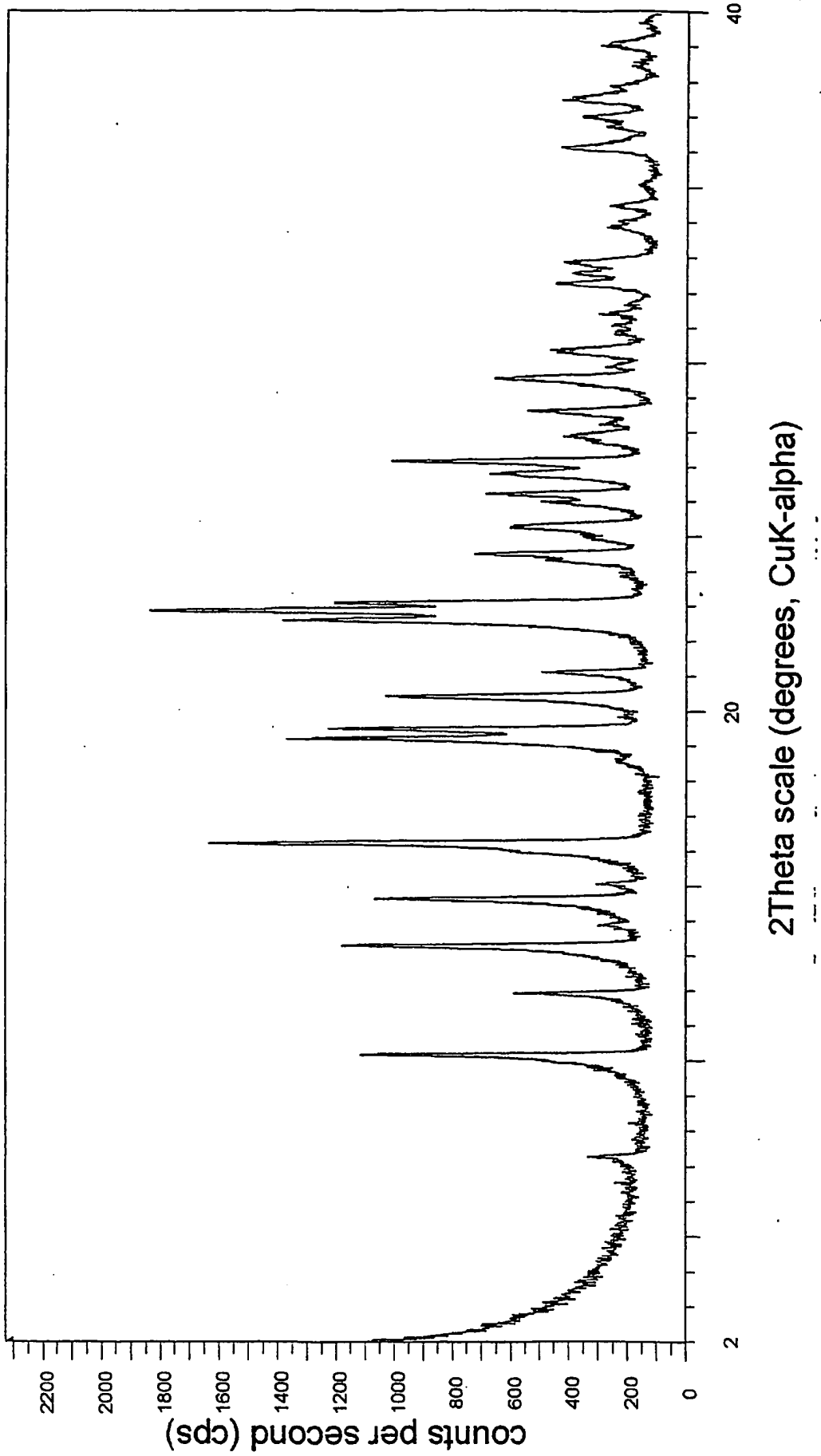
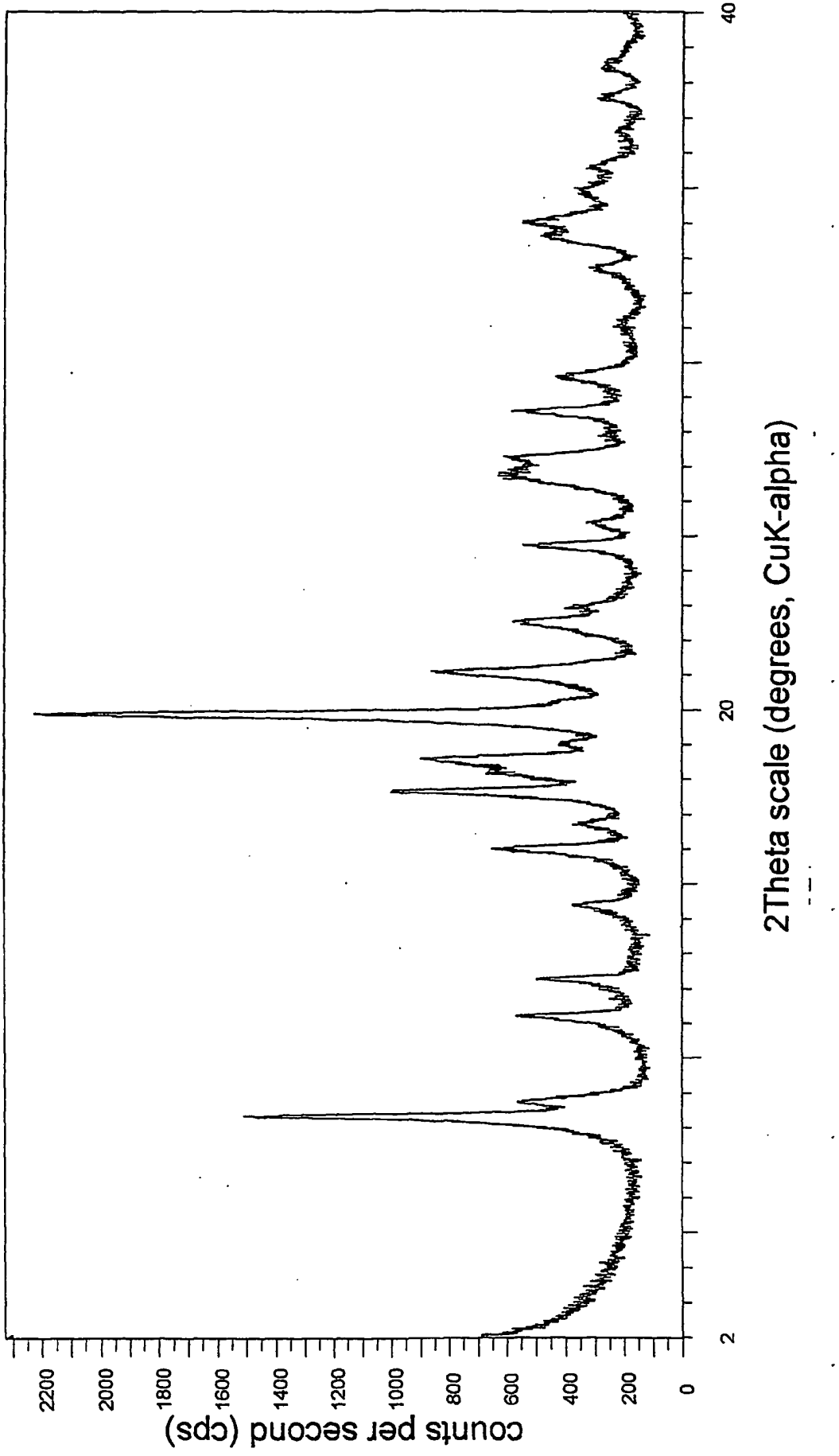


FIGURE 2

G-33166A



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 501/06, C07F 7/10, 7/18

A1

(11) International Publication Number: WO 00/63214

(43) International Publication Date: 26 October 2000 (26.10.00)

(21) International Application Number: PCT/EP00/03428

(22) International Filing Date: 14 April 2000 (14.04.00)

(30) Priority Data:

673/99	15 April 1999 (15.04.99)	AT
763/99	29 April 1999 (29.04.99)	AT
800/99	5 May 1999 (05.05.99)	AT
1042/99	14 June 1999 (14.06.99)	AT

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

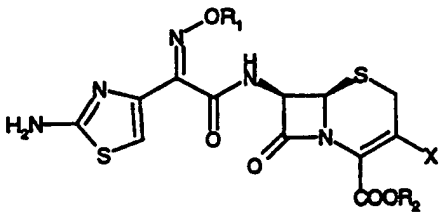
(71) Applicant *(for all designated States except US)*: BIOCHEMIE GESELLSCHAFT M B H [AT/AT]; A–6250 Kundl (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GERLACH, Benjamin [DE/AT]; Dorf Nr. 411, A–6252 Breitenbach (AT). LUDESCHER, Johannes [AT/AT]; Kleinsöll 101, A–6252 Breitenbach (AT). TOTSCHNIG, Klaus [AT/AT]; Biochemiestrasse 44/4, A–6250 Kundl (AT).

(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH–4002 Basel (CH).

(54) Title: BETA–LACTAM PRODUCTION



(I Abstract)

(57) Abstract

The present invention provides processes for the production of a compound of formula ($I_{Abstract}$) wherein X, R_1 and R_2 are substituents conventional in cephalosporin chemistry; especially a compound of formula ($I_{Abstract}$) is ceftriaxone, cefotaxime; e.g. in the form of a salt.

FOR THE PURPOSES OF INFORMATION ONLY

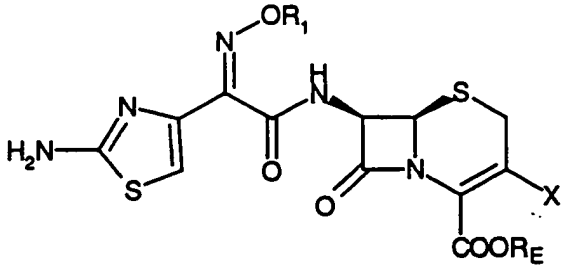
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Beta-lactam production

The present invention relates to the production of β-lactams, such as pharmaceutically active β-lactams, e.g. cephalosporins, such as ceftriaxone or similar compounds.

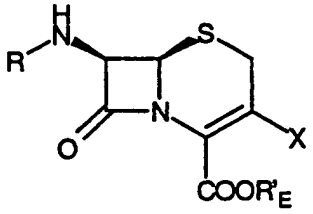
In one aspect the present invention provides a process for the production of a compound of formula



I

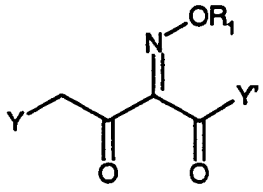
wherein X and R_1 are substituents useful in cephalosporin chemistry and R_E is hydrogen, a negative charge or together with the COO- group to which R_E is attached is an ester; e.g. ceftriaxone or cefotaxime; comprising

i) reacting a compound of formula



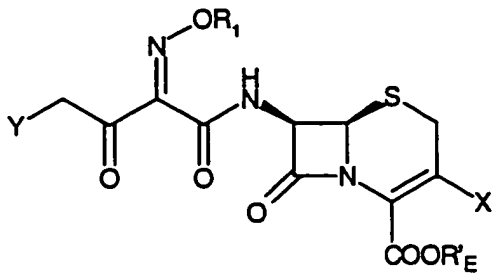
IV

wherein R is hydrogen or silyl, R'_E is silyl or together with the COO- group to which R_E is attached is an ester; and X is as defined above, with a compound of formula



III

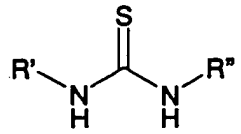
wherein Y is halogen, Y' is a group which forms a basis that a compound of formula III is in a reactive form; and R_1 is as defined above, to obtain a compound of formula



II

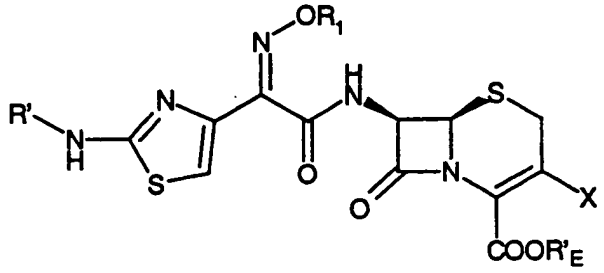
wherein Y, X, R'_E and R_1 are as defined above;

ii) reacting a compound of formula II wherein X, Y, R'_E and R_1 are as defined above, with a compound of formula



V

wherein R' is hydrogen or silyl and R" is silyl; to obtain a compound of formula



VI

wherein X, R_1, R' and R'_E are as defined above, and desilylating a compound of formula VI to obtain a compound of formula I; or

ii') desilylating a compound of formula II wherein Y, X, R'_E and R_1 are as defined above, and reacting a desilylated compound of formula II with thiourea in a solvent system containing organic solvent and water; e.g. and an alcohol; to obtain a compound of formula I;

e.g. a compound of formula I in free form; e.g. or a compound of formula I in the form of a solvate, or in the form of an ester or in the form of a salt; or in the form of an ester or in the form of a salt, and in the form of a solvate.

In another aspect the present invention provides a process for the production of a compound of formula I, wherein X, R_1 and R_E are as defined above, e.g. ceftriaxone or cefotaxime; comprising reacting a compound of formula II, wherein Y, X, R'_E and R_1 are as defined above,

with a compound of formula V wherein R' and R" are as defined above according to step ii) as defined above; or

desilylating a compound of formula II, wherein Y, X, R'_E and R_1 are as defined above, and reacting a desilylated compound of formula II with thiourea according to step ii') as defined above, to obtain a compound of formula I;

e.g. a compound of formula I in free form; e.g. or a compound of formula I in the form of a solvate, or in the form of an ester or in the form of a salt; or in the form of an ester or in the form of a salt, and in the form of a solvate.

A compound of formula I in free form, in the form of an ester and in the form of a salt; e.g. and in the form of a solvate; e.g. or in the form of a non-solvate, may be obtained.

A compound of formula I in free form, e.g. and in the form of a solvate or in the form of a non-solvate; may be converted in the form of an ester or in the form of a salt; e.g. and in the form of a solvate, or in the form of a non-solvate; and vice versa. A compound of formula I in the form of a solvate may be converted into a compound of formula I in the form of a non-solvate and vice versa. Conversion may be carried out according to a method as conventional, e.g. including a method as conventional.

It is one advantage of the present invention that a compound of formula II needs not to be isolated in the course of the reaction. It is another advantage of the present invention that a process of the present invention may be a one-pot process.

In a compound of formula I,

X is a substituent useful in cephalosporin chemistry. A substituent useful in cephalosporin chemistry includes e.g. a substituent according to a substituent conventional in cephalosporin chemistry, e.g. including a substituent conventional in cephalosporin chemistry. A substituent useful in cephalosporin chemistry includes a substitutent which is useful in pharmaceutically active cephalosporins; and a substitutent which is useful in intermediates for the production of pharmaceutically active cephalosporins. Preferably X is alkyl or alkenyl, more preferably methyl or ethenyl; e.g. including unsubstituted or substituted alkyl and alkenyl; e.g. unsubstituted alkyl and alkenyl, and alkyl and alkenyl substituted by alkoxy, heterocylcylthio, heterocyclylcarbonylthio; alkylcarbonyloxy, preferably methylcarbonyloxy; heterocyclyl;

R_1 is a substituent useful in cephalosporin chemistry. Preferably R_1 is unsubstituted or substituted alkyl, e.g. unsubstituted alkyl, or alkyl substituted by carboxyl. More preferably R_1 is methyl; carboxymethyl; or a group of formula $-C(CH_3)_2COOH$.

R_E is hydrogen, a negative charge or is, together with the COO- group to which R_E is attached, an ester group; e.g. an ester group useful in cephalosporin chemistry.

If R_E is a negative charge, the group X may contain a positive charge; e.g. in the form of a positively charged amine.

If R_E together with the COO- group to which R_E is attached is an ester group R_E preferably forms with the COO- group a physiologically hydrolysable and acceptable ester; e.g. R_E is a substituent useful in cephalosporin chemistry.

A compound of formula I may thus be in the form of a physiologically-hydrolysable and -acceptable ester. By physiologically-hydrolysable and -acceptable esters as used herein is meant an ester in which the COO- group together with R_E forms an ester which is hydrolysable under physiological conditions to yield an acid which is itself physilogically tolerable at dosages to be administered. The term "R_E together with the COO- group to which R_E is attached is an ester group" is thus to be understood as defining regular pro-drug forms of a compound of formula I. A group $-OR_E$ may be preferably a group which is easily hydrolysable under physiological conditions. Such esters may be administered preferably orally, since hydrolysis usually takes place under the influence of the digestive enzymes. Parenteral administration may be indicated if the ester per se is an active compound or, if hydrolysis occurs in the blood.

If not otherwise defined herein heterocyclyl includes e.g. 5 or 6 membered heterocyclyl; e.g. including a bicyclic ring system, e.g. of 10 to 12 carbon atoms; e.g. hetrocyclyl having 1 to 4 heteroatoms; e.g. selected from N,O or S; e.g. including unsubstituted heterocyclyl or substituted heterocyclyl, e.g. unsubstituted heterocyclyl or heterocyclyl substituted; e.g. by one or more substituents; e.g. by a substituent useful in cephalosporin chemistry; e.g. heterocyclyl substituted by alkyl, e.g. including (C_{1-4})alkyl; carboxyalkyl; carbonyl. Alkyl includes (C_{1-4})alkyl. Alkenyl includes (C_{2-4})alkenyl. Alkoxy includes (C_{1-4})alkoxy. Silyl includes trialkylsilyl, e.g. trimethylsilyl. Halogen (halo-) includes bromide, chloride, iodide.

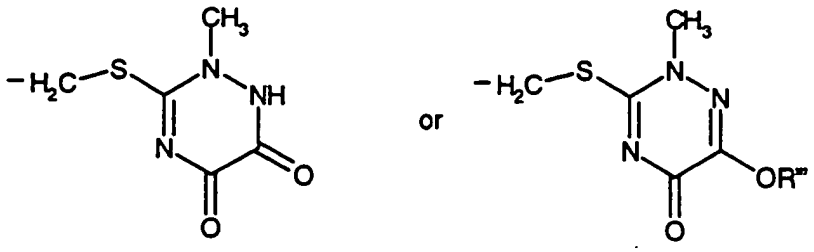
A solvent system or solvent (system) includes one or more individual solvents.

Preferably a compound of formula I is cefdinir (see e.g. Merck Index, 12th edition, item 1971), cefditoren (see e.g. Merck Index, 12th edition, item 1972), cefepime (see e.g. Merck Index, 12th edition, item 1973), cefetamet (see e.g. Merck Index, 12th edition, item 1974), cefixime (see e.g. Merck Index, 12th edition, item 1975), cefmenoxime (see e.g. Merck Index, 12th edition, item 1976), cefodizime (see e.g. Merck Index, 12th edition, item 1979), cefotaxime (see e.g. Merck Index, 12th edition, item 1983), cefpirome (see e.g. Merck Index, 12th edition, item 1990), cefpodoxime and cefpodoxime proxetil (see e.g. Merck Index, 12th edition, item 1991), ceftazidime (see e.g. Merck Index, 12th edition, item 191995), cefteram (see e.g. Merck Index, 12th edition, item 1996), ceftiofur (see e.g. Merck Index, 12th edition, item 1999), ceftriaxone (see e.g. Merck Index, 12th edition, item 2001), cefuzonam (see e.g. Merck Index, 12th edition, item 2003); more preferably a compound of formula I is ceftriaxone or cefotaxim.

A compound of formula I includes a compound of formula I in free form, in the form of an ester and in the form of a salt; e.g. and in the form of a solvate or in the form of a non-solvate.

Step i) may e.g. be carried out as follows:
Compounds of formulae III and IV are known and may be prepared according to a method as conventional. In a compound of formula III, Y' is a group which forms a basis that a compound of formula III is in a reactive form; e.g. including halogen, a group which forms together with the –C=O group to which Y' is attached an active ester, and a group which forms together with the
–C=O group to which Y' is attached a mixed anhydride.
If X and/or R_1 comprise silylatable groups (functions), such groups may be in silylated form in a compound of formulae II, IV and VI. If X and/or R_1 comprise silylated groups in a compound of formulae II or VI such groups are desilylated in step ii) or ii'). Preferably a compound of formula II or of formula VI contains one or more silyl groups.

In another aspect the present invention provides a compound of formula II wherein R'_E, R_1 and Y are as defined above; e.g. a compound of formula II, wherein preferably R'_E is silyl, R_1 is methyl and Y is defined as above; and X denotes a group of formula



wherein R''' is silyl.

Such compounds are new; are e.g. useful intermediates, e.g. in the production of pharmaceutically active cephalosporins; e.g. and may be obtained by reaction of a compound of formula III, wherein Y is halogen, e.g. bromo, chloro; and Y' is halogen, e.g. chloro; with a compound of formula IV wherein R'_E is silyl, and X is one of the above two mentioned groups; e.g. in an organic solvent (system).

Step ii) may be carried out as follows:
Thiourea may be silylated with a silylation agent in a solvent (system) inert under the reaction conditions. Appropriate silylation agent e.g. includes silylation agents according to conventional silylation agents, e.g. including conventional silylation agents, e.g. mono- or bissilylated amides, e.g. derived from formamides, acetamides or trifluoroacetamides; bis-(trimethylsilyl)-urea or hexamethyldisilazane, e.g. in combination with an acid; halosilanes, e.g. chlorsilanes, e.g. in combination with an acid acceptor, e.g. an amine, such as triethylamine, tert.octylamine. A solvent (system) includes e.g. halogenated, e.g. chlorinated, hydrocarbons, such as dichloromethane; esters, e.g. ethyl acetate; and ethers; e.g. tetrahydrofuran. A compound of formula V, wherein R' and R" are as defined above, may be obtained.

In another aspect the present invention provides a compound of formula V, wherein R' is hydrogen or tri(C_{1-4})alkylsilyl, e.g. trimethylsilyl; and R" is tri(C_{1-4})alkylsilyl; e.g. trimethylsilyl.

Compounds of formula V are useful intermediates, e.g. in the production of pharmaceutically active cephalosporins. If an equivalent amount or more of a silylation agent is used in respect with the two possible reaction sites in thiourea, a compound wherein both, R' and R", are tri(C_{1-4})alkylsilyl may be obtained. If an amount below the equivalent amount is used in respect with the two possible reaction sites in thiourea, e.g. an amount equivalent in respect with one

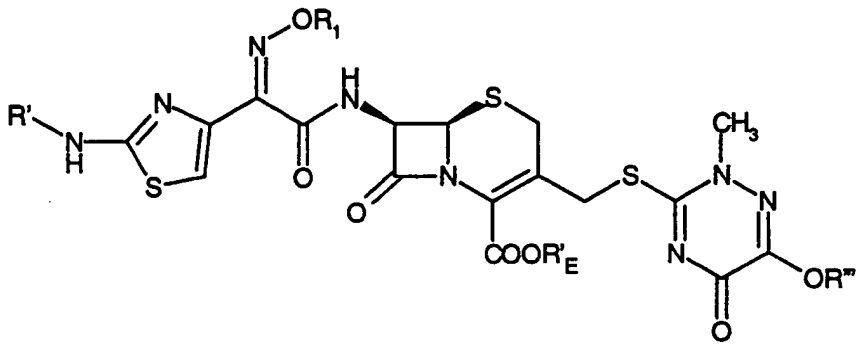
of the possible reaction sites in thiourea, a compound of formula V may be obtained wherein R' is hydrogen and R" is tri(C_{1-4})alkylsilyl.

A compound of formula V may be obtained in the form of a mixture of a compound of formula V wherein R' is hydrogen and R" is tri(C_{1-4})alkylsilyl and a compound of formula V wherein both, R' and R", are tri(C_{1-4})alkylsilyl. A compound of formula V may be isolated, e.g. according to a method as conventional. In a reaction according to the present invention a compound of formula V is preferably not isolated.

E.g. according to step ii) a compound of formula II wherein R'_E, R_1, X and Y are as defined above; e.g. wherein in a group X and /or in a group R_1 silyl groups may be present; may be reacted with a compound of formula V, wherein R' and R" are as defined above, e.g. produced as described above or in the examples. That reaction may be carried out in a solvent (system), e.g. a solvent (system) as described above in the production of a compound of formula V. An acid acceptor may be present, e.g. to bind an acid, e.g. formed in the course of the reaction; e.g. including mono- or bissilylated amides, e.g. as described above; or amines, e.g. trialkylamines, such as N,N-diispropylethylamine.

A compound of formula VI wherein R'_E is as defined above; e.g. wherein in a group X and/or R_1 silyl groups may be present; may be obtained.

In another aspect the present invention provides a compound of formula



e.g. which is a compound of formula VI; wherein R_1 is as defined above, e.g. methyl; and R', R'_E and R"' are tri(C_{1-4})alkylsilyl, e.g. trimethylsilyl; e.g. useful in the production of ceftriaxone, e.g. or similar compounds.

Desilylation of a compound of formula VI obtained in a process according to the present invention may be e.g. either carried out according to a method as conventional, e.g. by treatment with an alcohol and/or water and isolating a compound of formula I obtained; or may be carried out in the course of the isolation of a compound of formula I; e.g. a compound of formula I may directly be isolated from the reaction mixture containing a compound of formula VI comprising silyl groups, in free form, in the form of an ester or the form of a salt, and e.g. in the form of a solvate or in the form of a non-solvate; e.g. without isolating a compound of formula VI. This may be carried out e.g. according to a method as conventional; e.g. using appropriate extraction and isolation steps, such as:

E.g. Completing desilylation before isolating a compound of formula I;

e.g. Choosing optimal pH conditions in respect with stability and isolation of a compound of formula I, e.g. by use of buffer solutions, alkaline solutions or ammonium salt solutions of organic acids such as carbonates, carboxylates, phosphates, phosphonates and borates;

e.g. Choosing optimal conditions in respect with the solubility of a compound of formula I,

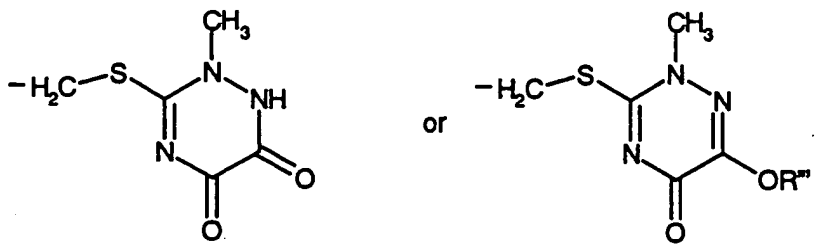
e.g. Choosing optimal solvent (system) conditions; e.g. beside water, organic solvents may be used, e.g. alcohols, such as (C_{1-4})-alcohols, such as 2-propanol; ketones, e.g. acetone; nitriles, e.g. acetonitrile; esters, e.g. methyl acetate; ethers, e.g. tetrahydrofuran; and amides, e.g. dimethylformamide;

e.g. Choosing an aqueous/organic solvent system which may optimize the separation of side products.

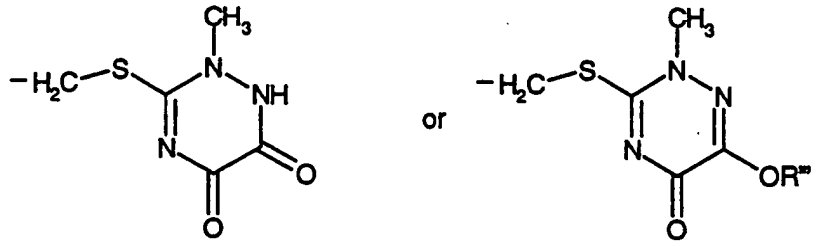
E.g. ceftriaxone in the form of a disodium salt; e.g. and in the form of a hemiheptahydrate, may be directly obtained from a reaction mixture containing a corresponding silylated ceftriaxone of formula VI, e.g. by treating the reaction mixture containing a silylated ceftriaxone, e.g. produced according to a process of the present invention, with a mixture of water and organic solvent which is miscible with water, e.g. acetone; and a base, e.g. a sodium source; e.g. sodium 2-ethylhexanoate; and with a mixture of water and an organic solvent which is able to from a two-phase system with water, e.g. dichloromethane. The pH of the mixture obtained is adjusted to about 6.5, e.g. 6.5; by addition of a base, e.g. sodium bicarbonate. A two-phase system is formed. The organic phase is separated off and the pH of the aqueous phase is adjusted to a pH of about 3, e.g. 3; by addition of an acid, e.g. hydrochloric acid. A precipitate (ceftriaxone in free form) is obtained and filtrated off. The precipitate obtained is suspended in a mixture of water and organic solvent which is miscible

with water, e.g. acetone; and the pH of the mixture obtained is is adjusted to about 6.5, e.g. 6.5; by addition of a sodium source, e.g. a sodium salt, e.g. sodium bicarbonate. A solution is obtained from which ceftriaxone In the form of a disodium salt; e.g. and in the form of a hemiheptahydrate; crystallizes and may be isolated, e.g. by filtration. E.g. by addition of further organic solvent, e.g. acetone; crystallization may be completed.

In another aspect the present invention provides a process for the production of ceftriaxone in the form of a disodium salt, e.g. and in the form of a hemiheptahydrate; e.g. in high purity; e.g. in crystalline form; comprising reacting a compound of formula II wherein Y is as defined above, R_1 is CH_3, R'_E is silyl; and X is a group of formula



wherein R''' is as defined above, with a compound of formula V, wherein R' and R'' are as defined above to obtain a compound of formula VI, wherein R'_E is silyl; R_1 is CH_3, R' is as defined above and X is a group of formula



wherein R''' is as defined above; and

i) treating the reaction mixture obtained with water/organic solvent which is miscible with water, a base and with water/organic solvent which is able to form a two-phase system with water;

ii) adjusting the pH of the mixture obtained to about 6.5; e.g. by addition of a base;

iii) separating off the organic solvent from the two-phase system obtained;

iv) adjusting the pH of the aqueous phase obtained to a pH of about 3; e.g. by addition of an acid,

v) filtrating off the precipitate formed;

vi) suspending the precipitate obtained in a mixture of water and organic solvent which is miscible with water;

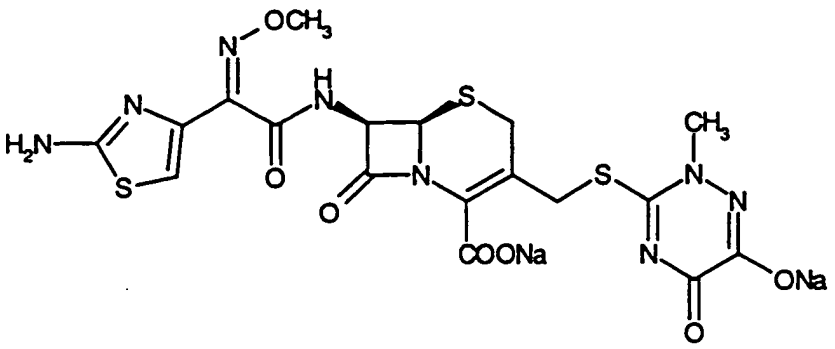
vii) adjusting the pH of the mixture obtained to about 6.5; e.g. by addition of a base; e.g. and adding acetone to the mixture obtained to complete crystallisation; and

viii) isolating ceftriaxone in the form of a disodium salt; e.g. and in the form of the hemiheptahydrate.

A process for the production of ceftriaxone in the form of a disodium salt according to the present invention may be e.g. carried out as follows:

A compound of formula II wherein R'_E, R_1, X and Y are as described above, e.g. obtained as described above; is desilylated, e.g. according to a method as conventional, e.g. by treatment with alcohol and/or water. A compound of formula II which is desilylated may be obtained and may be reacted, e.g. without isolation from the reaction mixture obtained; with thiourea in a solvent mixture (system) comprising water; e.g. in organic solvent, e.g. a solvent which is able to form a two-phase system with water, including halogenated, e.g. chlorinated hydrocarbons, e.g. dichloromethane, esters, e.g. acetic acid (C_{1-4})alkyl esters; ethers, e.g. diisopropylethers; and in the presence of water; and e.g. in the presence of alcohols, such as an (C_{1-4})alcohol, e.g. ethanol or isopropanol. Preferably an alcohol is present, e.g. in an appropriate amount; e.g. including amounts of 5% to the double volume of the volume of the total solvent system used, e.g. in case of dichloromethane present as an organic solvent, including amounts of 5% to 30 % of the volume of the total solvent system used. A base, e.g. an amine, e.g. triethylamine, may be present; e.g. in order to neutralize an halogenic acid set free in the course of the reaction. A compound of formula I may be obtained; e.g. in free form or in the form of a salt; and e.g. in the form of a solvate or in the form of a non-solvate; and may be isolated and e.g. may be purified; e.g. according to a method as conventional; e.g. or according to a method as described above.

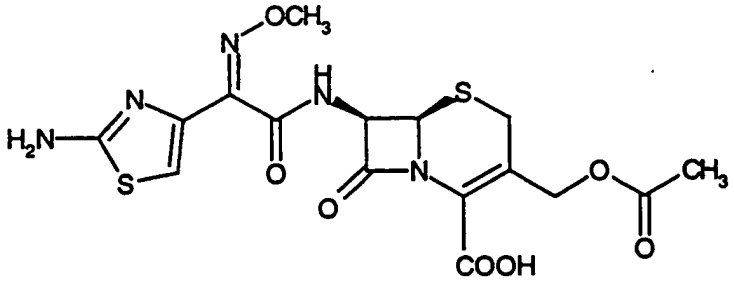
In another aspect the present invention provides a process for the production of ceftriaxone in the form of a disodium salt, e.g. of formula



IA

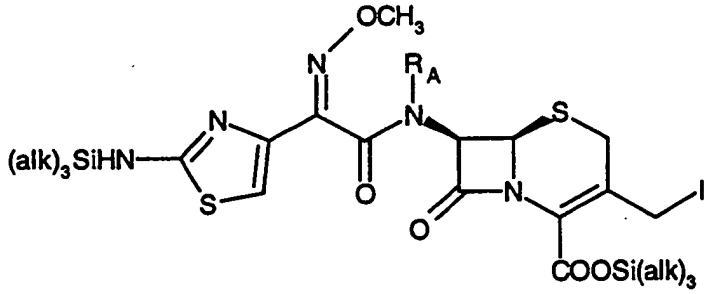
comprising

i) silylating a compound of formula



IIA

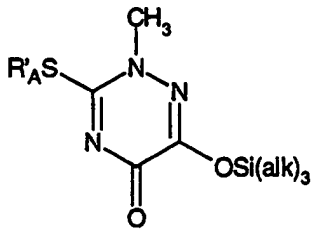
or a compound of formula IIA in the form of a salt and iodinating; e.g. a compound obtained in silylation; to obtain a compound of formula



IIIA

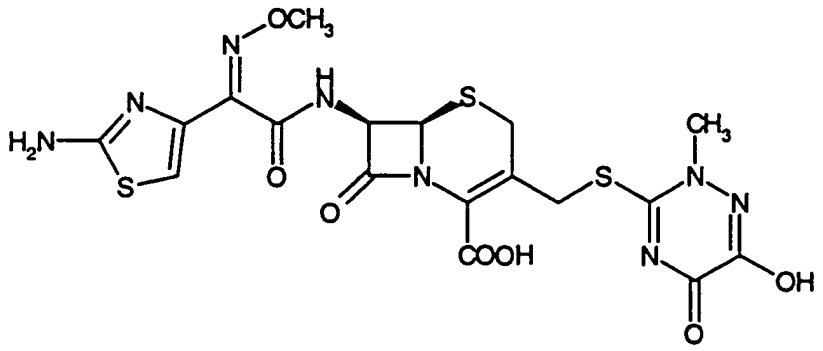
wherein R_A is hydrogen or trialkylsilyl; e.g. trimethylsilyl; and alk is alkyl, e.g. methyl;

ii) reacting a compound of formula IIIA obtained in step i) with a compound of formula



IVA

wherein R'_A is hydrogen or trialkylsilyl, e.g. trimethylsilyl; and desilylating; e.g. a compound obtained by reaction of a compound of formula IIIA with a compound of formula IVA;, to obtain a compound of formula



VA

iii) isolating a compound of formula VA obtained in step ii) from the reaction mixture; and

iv) converting a compound of formula VA obtained in step iii) into ceftriaxone in the form of a disodium salt; e.g. and in the form of a hemiheptahydrate.

A process for the production of a compound of formula VA according to the present invention may be carried out as follows:

Step i) may be carried out according to a method as conventional and is preferably carried out as follows:

In step i) a compound of formula IIIA may be obtained by treating a compound of formula IIA (e.g. the compound 7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-(acetyloxy) methyl-3-cephem-4-carboxylic acid, i.e. cefotaxime in free form) or a compound of formula IIA in the form of a salt; e.g. in the form of an ammonium salt; or in the form of a sodium salt (sodium cefotaxime); preferably sodium cefotaxime; with a silylation agent and an iodination agent in a solvent (system).

Preferably sodium cefotaxime is used, e.g. in view of the fact, that

- cefotaxime in free form is a strongly solvating molecule, e.g. acetone and ethanol solvates of cefotaxime are known;
- cefotaxime in free form may contain considerable amounts of water;

whereas sodium cefotaxim is poorly solvating and contains usually less amounts of solvent than cefotaxime in free form. Thus, if sodium cefotaxime is used instead of cefotaxime in free form, less silylation agent, e.g. trialkylsilylation; agent which may be reactive in respect with solvent (system), e.g. water and acetone, may be used.

Appropriate silylation agents include silylation agents usable according to conventional silylation processes; e.g. halosilanes, such as iodotrialkylsilane, e.g. iodotrimethylsilane (TMIS), e.g. in the presence of a nucleophile base; silylated amides, e.g. N,O-bis-(trimethylsilyl)-trifluoracetamide (BSTFA), N-methyl-N-trimethylsilyltrifluoracetamide (MSTFA); silazanes, e.g. 1,1,3,3,3-hexamethyldisilazane (HMDS); silylated ureas, such as bis-(trimethylsilyl)-urea (BSS), N,N'-bis-(trimethylsilyl)-urea (BSU); or a mixture of two or more of silylation agents; e.g.; a mixture of BSTFA or MSTFA or BSS or BSU with HMDS; preferably a mixture of BSTFA or MSTFA or BSS or HMDS with TMIS a mixture of BSTFA or MSTFA or BSS or HMDS with TMIS. The choice of a specific silylation agent may be important to enhance e.g. yield and purity of a desired compound of formula IIIA. If sodium cefotaxime is used for silylation preferably BSTFA, BSS or HMDS in combination with TMIS may be used. If cefotaxime in free form is used for silylation preferably HMDS, e.g. in the present of a silylation catalyst, e.g. including a silylation catalyst according to a conventional process; may be used. Preferably silylation is carried out before iodination.

An iodination agent includes an iodination agent usable in iodination reactions, e.g. according to a conventional iodination reaction, e.g. an iodination agent conventional in cepholosporin chemistry, e.g. an iodotrialkylsilane, preferably TMIS, e.g. produced in situ from iodine and hexamethlydisilane in dichloromethane. Preferably per mol of cefotaxime in free form or in the form of a salt 1.5 to 2.5 mol of iodination agent may be used. Iodination may be completed after silylation, e.g. a first amount of TMIS may be added to a compound of formula IIA preferably for silylation; and a second amount thereafter may be added for completing iodination.

To obtain a compound of formula IIIA wherein R'_A denotes trialkylsilyl, e.g. after iodination, a corresponding higher amount of a silylation agent may be used than for the case where R'_A denotes hydrogen.

An appropriate solvent (system) includes a solvent (system) inert under the reaction conditions, e.g. halogenated, e.g. chlorinated hydrocarbons, e.g. dichloromethane; nitriles; preferably dichloromethane.

A compound of formula IIIA obtained via silylation and iodination of a compound of formula IIA may be isolated, e.g. according to a process as conventional; but is preferably further reacted without isolation with a compound of formula IVA.

In step ii) a compound of formula IIIA ; e.g. as obtained in step i); is reacted with a compound of formula IVA, e.g. silylated 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin; e.g. to obtain a compound of formula VA in a silylated form; and desilylating a compound of formula VA in a silylated form, to obtain a compound of formula VA; e.g. 7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]-3-cephem-4-carboxylic acid; in a solvent (system). Step ii) may be carried out according to a method as conventional and preferably may be effected as follows:

A compound of formula IVA which contains silylatable oxygen functions and which has a better solubility, e.g. in organic solvent (system); in a silylated form than in a non-silylated form, may be obtained by silylation of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin. Appropriate silylation agents include e.g. silylated amides; such as N,O-bis-(trimethylsilyl)-acetamide (BSA), N-methyl-N-trimethylsilyl-acetamide (MSA), BSS, BSU; or a silylation agent as appropriate in step i) for silylating a compound of formula IIA; of the present invention; preferably BSA. An appropriate solvent (system) includes solvent (system) inert under the reaction conditions, e.g. halogenated, e.g. chlorinated hydrocarbons, e.g. dichloromethane; nitriles, e.g. acetonitrile; amides, e.g. dimethylacetamide; esters, e.g. ethylacetate; and ethers, e.g. tetrahydrofuran: preferably dichloromethane. BSA as a silylation agent together with dichloromethane as a solvent are preferred; e.g. in view of the finding of a quick silyation and easy solvent recovery.

Per mol of a compound of formula IIIA about 1 mol of a compound of formula IVA; e.g. or more; may be used. Preferably per mol of of a compound of formula IIA, or of a compound of formula IIA in the form of a sodium salt 0.9 to 1.1 of a compound of formula VIA may be appropriate.

A compound of formula VA may be obtained which is isolated according to step iii) of the present invention.

Preferably steps i) and ii) may be carried out as follows:

Sodium cefotaxim in dichloromethane is silylated with a mixture of BSTFA or BSS with TMIS. 1.5 to 2.5 mol per mol of sodium cefotaxime are added to the reaction mixture obtained in silylation at appropriate temperatures, e.g.at a temperature from –20° to 20°C; preferably from 0° bis 10 °. A compound of formula IIIA is obtained and is reacted with a compound of formula IV, produced by reaction of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin with BSA in dichloromethane. A compound of formula VA in a silylated form may be obtained.

Desilylation of a compound of formula VA in a silylated form may be carried out according to a method as conventional, e.g. by treatment with water and/or alcohol, e.g. in the presence of organic solvent (system); e.g. solvent originating from the reaction of a compound of formula IIIA with a compound of formula IVA; and e.g. in the presence of a base, preferably sodium acetate or an amine. More preferably a reaction mixture obtained in step ii) is mixed with an alcoholic solution of sodium acetate and water. A compound of formula VA may be obtained.

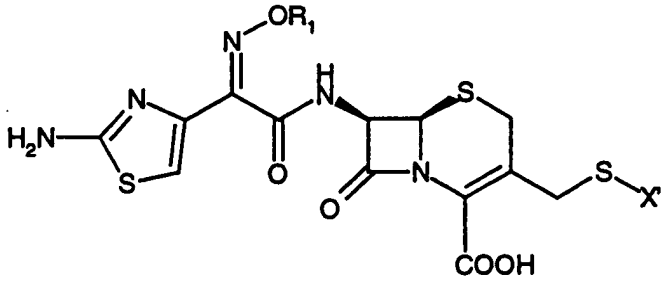
Step iii), i.e. isolation of a compound of formula VA, may be effected according to a method as conventional and is preferably effected as follows:
The pH of a reaction mixture obtained in step ii) may be adjusted to (about) 4 to 7, preferably to (about) 6 to 6.5, e.g. either after desilylation of a compound of formula VA in a silylated form; or during desilylation, e.g. in case that a base is used in the desilylation step; preferably after desilylation. A reducing agent may be added to the reaction mixture, e.g. in order to remove reduceable components present in the reaction mixture, e.g. iodine; e.g. including thiosulphate, bisulfite, ascorbinic acid. Water and an organic solvent, which is able to form a two-phase system with water, e.g. dichloromethane, is added to the mixture obtained and a two-phase system is formed. The phases are separated and the organic phase is dismissed. In order to remove colored impurities the aqueous phase may be treated with charcoal. After charcoal removal, the pH of the aqueous phase may be adjusted to (about) 2.0 to 3.5, e.g. 3.0. A compound of formula VA may precipitate and may be isolated, e.g. by filtration.

According to conventional methods in ceftriaxone production a compound of formula VA is usually not isolated from a reaction mixture containing it, but isolated in the form of a salt, e.g. directly as a compound of formula IA; or in the form of another salt, e.g. in the form of a dibenzylethylendiamine salt. We have found that isolation of a compound of formula VA according to the present invention surprisingly may improve the quality, e.g. purity, side product-profile (e.g. less side products), content, color; and may improve surprisingly the crystallisation behaviour; of a compound of formula IA, produced from an isolated compound of formula VA, e.g. compared with direct production of a compound of formula IA from a compound of formula VA without isolation of a compound of formula VA.

According to step iv) a compound of formula VA isolated in step iii) is converted into a compound of formula IA, e.g. ceftriaxone in the form of a disodium salt. Step iv) may e.g. be carried out according to a conventional method and is preferably carried out as follows: Preferably a compound of formula VA in isolated form, e.g. isolated as described in step iii), is further purified before conversion into a compound of formula IA. Further purification includes e.g. dissolution in an alcohol, e.g. methanol and charcoal treatment of the mixture obtained. For conversion a compound of formula VA is treated in a solvent (system) with a sodium source to obtain a pH of the mixture of (about) 5.0 to 7.0. A solvent (system) includes a mixture of organic solvent, preferably acetone; and water; e.g. in a range of organic solvent:water of e.g. 1:1 to 10:1; such as 3:1 to 8:1; e.g. 5:1. A sodium source includes e.g. a sodium salt, e.g. a sodium salt of an acid, e.g. sodium hydroxide, carbonate, bicarbonate, acetate. Ceftriaxone in the form of a disodium salt, e.g. in the form of a hemiheptahydrate; may crystallize. Crystallization may be completed by addition of organic solvent, e.g. by addition of further acetone.

A compound of formula IA, i.e. ceftriaxone in the form of a disodium salt may be obtained and may be isolated in surprising high purity.

In another aspect the present invention provides a process for the production of a compound of formula

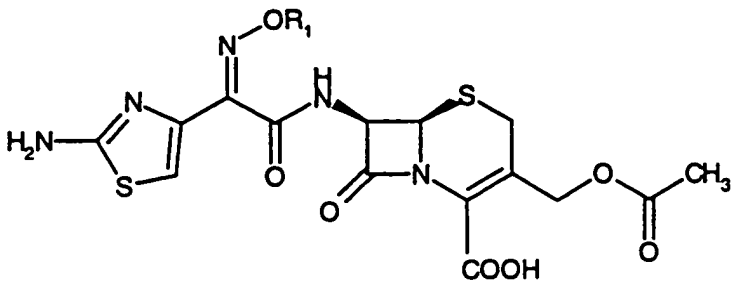


IB

wherein X' and R_1 are substituents useful in cephalosporin chemistry; e.g. a compound of formula I is ceftriaxone; e.g. in free form, in the form of an ester or in the form of a salt; e.g. and in the form of a solvate; or in the form of a non-solvate;

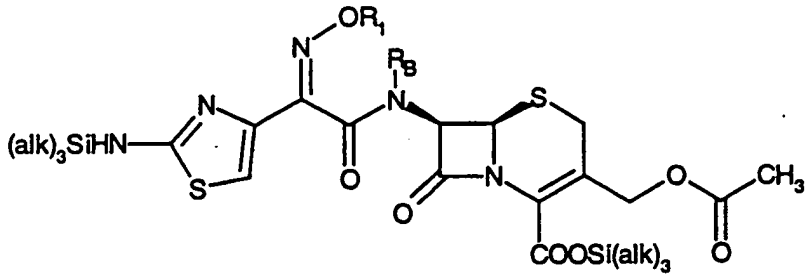
comprising

i) silylating a compound of formula



IIB

or a compound of formula IIB in the form of a salt, to obtain a compound of formula



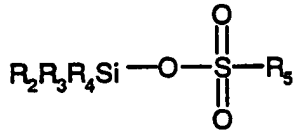
IIIB

wherein R_B is hydrogen or trialkylsilyl, and alk is alkyl;

ii) reacting a compound of formula IIIB with a compound of formula

$R'_BS\text{-}X'$ IVB

wherein R'_B is hydrogen or trialkylsilyl and X' is as defined above, in the presence of a compound of formula



VB

wherein R_2, R_3 and R_4 independently of each another are aryl or alkyl, and R_5 is alkyl or aryl; e.g. trimethylsilyl-trifluoromethanesulfonate; and

iii) isolating a compound of formula IB from the reaction mixture obtained in step ii).

In a compound of formula IB, X' and R_1 are substituents useful in cephalosporin chemistry; e.g. R_1 is alkyl, e.g. methyl; and X' is heterocyclyl or heterocyclylcarbonyl, preferably heterocyclyl. A compound of formula IB is preferably ceftriaxone.

A compound of formula IIB is e.g. 7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-(acetyloxy)methyl-3-cephem-4-carboxylic acid (cefotaxime in free form). A compound of formula II may be in free form or in the form of a salt, e.g. an ammonium salt or a sodium salt, preferably in the form of a sodium salt (sodium cefotaxime).

In process step i) a compound of formula IIB is silylated with a silylation agent to obtain a compound of formula IIIB. Process step i) may e.g. be carried out according to a method as conventional. A preferred silylation agent includes e.g.

- if a compound of formula II is used (cefotaxime in free form) preferably HMDS, BSTFA, MSTFA, e.g. in any combination;
- if a compound of formula IIB is used in the form of the sodium salt (sodium cefotaxime) preferably BSS, BSTFA, HMDS, e.g. in in the presence of a halotrialkylsilane, such as trimethylchlorsilan (TMCS).

Appropriate solvent (system) in the production of a compound of formula IB in a silylated form according to the present invention include preferably solvent (system) which may advantageously be used in all reaction steps i) to ii); e.g. solvent (system) which is inert during the whole reaction sequence; e.g. and which is compatible under the reaction conditions. Appropriate solvent (system) includes halogenated, e.g. chlorinated hydrocarbons, e.g. dichloromethane, aliphatic and aromatic hydrocarbons, e.g. cyclohexane, toluene; nitriles, e.g. acetonitrile, e.g. including mixtures of individual solvents as mentioned above; preferably dichloromethane, cyclohexane; toluene.

A compound of formula IIIB may be obtained and may be isolated from the reaction mixture, e.g. according to a method as conventional; a compound of formula IIIB is preferably not isolated from the reaction mixture but further reacted in step ii).

Process step ii) may be carried out as follows:

A compound of formula IIIB is reacted with a compound of formula IVB in the presence of a compound of formula VB.

A compound of formula IVB may be obtained by silylation of a compound of formula IVB which is in a non-silylated form. Compounds of formula IVB and compounds of IVB in a non-silylated form are known or may be prepared e.g. according to a method as conventional. Silylation of a compound of formula IV in a non-silylated form may e.g. be carried out according to a method as conventional. The group X' in a compound of formula IVB may comprise silylatable functions which are preferably silylated in the course of silylation of a compound of formula

IVB. Preferred solvents include solvent as described in step i) above. Preferred silylation agents include e.g. HMDS, BSU, 2-trimethylsilyl-1-oxazolidinone (TMSO), TMCS, e.g. in the presence of a base; BSTFA, BSA; preferably BSTFA, which is highly reactive in the silylation of the thiol function and other silylatable functions, e.g. as present in a group X'.

Compounds of formula VB are known or may e.g. be prepared according to a method as conventional. The choice of a specific compound of formula VB may be dependent on the reactivity and availability of a compound of formula VB. E.g. trialkylsilyl-sulfonic acid esters; trimethylsilyl-trifluoromethanesulfonate (TMSTf), t-butyl-dimethylsilyl-trifluoromethansulfonate, trimethylsilyl-nonafluorobutanesulfonate, trimethylsilyl-methanesulfonate or trimethylsilyl-benzenesulfonate are commercially available.

Preferred compounds of formula VB include compounds of formula VB, wherein R_2, R_3 and R_4 independently of each another are aryl or alkyl, preferably alkyl; and R_5 is alkyl, preferably perfluorinated alkyl, e.g. $-CF_3$. Preferably R_5 is a strong electron withdrawing (electrophilic) substituent, e.g. perfluorinated alkyl; e.g. perfluorinated sulfonates; e.g. trifluorosulfonate; or aryl, carrying substituents which are strong electron withdrawing (electrophilic) substitutents; e.g. perfluorinated alkyl, perfluorinated sulfonates, e.g. methanesulfonates; nitro groups. A preferred compound of formula VB is trimethylsilyl-trifluoromethanesulfonate.

A compound of fromula IIIB and a compound of formula IVB, e.g. commonly silylated in one pot; may be treated in a solvent (system); e.g. as described above; with a compound of formula VB; to obtain a compound of formula IB in a silylated form.

According to the present invention there are involved several silylation steps. In respect with silylation agents the following comments may be of interest:

The choice of the silylation agent may influence the reaction e.g. in view of the different silylated compounds which are used. E.g. a compound of formula VB is a strong silylation agent itsself and may thus silylate silylatable functions in molecules involved in the reaction sequence in the production of a compound of formula IB in a silylated form according to the present invention. In order to minimize the necessary amount of a compound of formula VB, it may be advantageous to achieve high silylation grades; i.e. silylation as complete as possible; in the production of a compound of formulae IIIB and IVB; although the reaction according to the present invention also works if compounds of formulae IIIB and IVB are incompletely silylated; e.g.if correspondingly the amount of a compound of formula VB is enhanced.

It is also advantageous to use such silylation agents in the silylation of a compound of formula IIIB and/or IVB, which; or which metabolites therof obtained after reaction; do not disturb the function of a compound of formula VB, e.g. by reaction with a compound of formula VB; e.g. which do not react with a compound of formula VB.

As already described above it should also be considered that the choice of a highly appropriate silylation agent may be dependent, whether a compound of formula IIB is used as such or in the form of a salt.

X' in a compound of formula IIB may further contain silylatable functions, which preferably should be already in a silylated form, e.g. as complete as possible, before a compound of formula VB is added to the reaction mixture.

The process of the present invention may be carried out e.g. in a one-pot reaction; e.g. a compound of formula IIB and a compound of fromula IVB may be silylated commonly and may be reacted in the same pot with a compound of formula VB, e.g. to obtain a compound of formula IB in a silylated form.

Corresponding to the silylation grade achieved in a compound of formulae IIIB and IVB; including the silylation grade of a group X' comprising silylatable functions in a compound of formula IIIB; the necessary amount of a compound of formula VB may be determined and may be added in step ii) of the process of the present invention.

Process step iii) may be carried out according to a method as conventional and is preferably carried out as follows:

The reaction mixture obtained after reaction of the compouds of formulae IIIB with IVB in the presence of a compound of formula VB; e.g. to obtain a compound of formula IB in a silylated form; is treated in aqueous or alcoholic solvent system, e.g. in the presence of an organic solvent; e.g. including neutralization of the reaction mixture with a base.

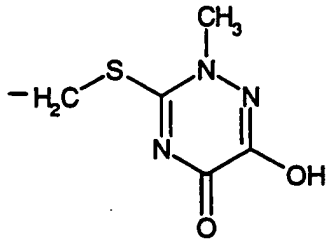
Preferably a desilylation step is carried out; e.g. according to a method as conventional in desilylation reactions. E.g. preferably a base is added, e.g. an alkali salt of a weak acid, e.g. sodium acetate; or an amine; to a reaction mixture obtained in step ii). The base may be dissolved in an alcohol, e.g. methanol; e.g. comprising water. A precipitate comprising a compound of formula IB may be formed upon addition of the base.

E.g. a compound of formula IB may be directly isolated by isolation of the precipitate formed; or via extraction steps. For isolation via extraction steps water and an organic solvent which is able to form a two-phase system with water may be added to the mixture obtained by addition

of a base to a reaction mixture obtained in step ii). A two-phase system may be obtained and the pH of the mixture obtained may be adjusted and a compound of formula IB may be extracted into the aqueous phase. The aqueous phase may be purified by charcoal treatment. The pH of the aqueous phase may be adjusted to an acidic pH, e.g. an pH from 2.0 to 3.5 and a compound of formula IB may precipitate and may be isolated according to a method as conventional.

A compound of formula IB may be isolated in free form, or in the form of a salt from the reaction mixture; e.g. and in the form of a solvate. A compound of formula IB in free form, optionally in the form of a solvate; may be converted in a compound of formula IB in the form of a salt; preferably in the form of a pharmaceutically acceptable salt; e.g. and in the form of a solvate. Precipitation of a compound of formula IB in free form may also be cicumvented, if desired. E.g. if a compound of formula IB in the form of a salt, e.g. a sodium salt, is desired to be isolatedd, a salt forming agent, e.g. including a sodium salt forming agent, e.g. sodium bicarbonate; may be added to an aqueous solution containing a compound of formula IB in free form and a compound of formula IB in the form of a salt, e.g. and in the form of a solvate; may be isolated from the reaction mixture. Alternatively a compound of formula IB may be isolated from the reaction mixture and may be converted in the form of a salt after isolation.

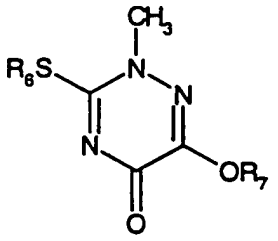
In a preferred embodiment of the present invention X' in a compound of formula IB denotes a group of formula



e.g. a compound of formula IB is ceftriaxone.

Ceftriaxone is preferably produced as follows:

A suspension of sodium cefotaxime in dichloromethane is cooled and silylated with BSS; e.g. 2 to 4 molequivalents BSS per mol of sodium cefotaxime (Solution A); e.g. to obtain a compound of formula III. A suspension of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin in dichloromethane is silylated with BSTFA, e.g. 1 to 5 molequivalents BSTFA per mol of sodium cefotaxime; to obtain a compound of formula VIIa or VIIb; or a mixture of a compounds of formula VIIa and VIIb:



VIIa: R_6=H, R_7=Si$(CH_3)_3$
VIIb: R_6,R_7=Si$(CH_3)_3$

(Solution B).

Solutions A and B are combined and 1 to 10 molequivalents of TMSTf are added per mol of sodium cefotaxime to the combined solutions.

Alernatively cefotaxime in free form and 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin are commonly silylated in dichlormethane and TMSTf is added; e.g. 1 to 10 molequivalents TMSTf per mol of cefotaxime in free form; to the mixture obtained.

The reaction mixture obtained is combined with an aqueous and/or alcoholic mixture of water and sodium acetate or triethylamine. A precipitate may be formed and either the precipitate comprising ceftriaxone is filtrated off and ceftriaxone is isolated in the form of a precipitate; or a solvent which is able to form a two-phase system with water, e.g. dichloromethane; is added to the mixture obtained upon addition of an aqueous and/or alcoholic mixture of water and sodium acetate or triethylamine. A two-phase system is obtained and ceftriaxone is extracted into the aqueous phase, e.g. after pH adjustment to 5 to 7, preferably to 6 to 6.5 by addition of a base, e.g. a sodium salt of a weak acid, e,g, sodium bicarbonate or sodium acetate. The phases are separated and the aqueous phase is purified by charcoal treatment. E.g. in order to separate off water soluble contents from ceftriaxone, the pH of the aqueous phase may be adjusted to 1.0 to 3,5, e.g. 3.0. Ceftriaxone in free form may precipitate and may be filtrated off.

Ceftriaxone obtained may be further purified by dissolution in an alcohol, e.g. methanol or propylene glycol; and charcoal treatment. Low boiling alcohol, e.g. methanol may be evaporated off from the filtrate obtained after charcoal treatment. The residue obtained, e.g. containing still alcohol, may be converted into ceftriaxone in the form of a disodium salt, e.g. by suspending ceftriaxone in free form in a mixture of acetone and water and adjusting the pH of the mixture obtained to 4 to 8, preferably to 5.8 in the presence of a sodium source; e.g. the sodium salt of a weak acid, e.g. sodium acetate or sodium bicarbonate. Crystalline ceftriaxone in the form of a disodium salt, e.g. in the form of a heptahydrate, may precipitate and may be isolated. Ceftriaxone in the form of a disodium salt may be obtained in high quality

In the following examples all temperatures are given in degree Celsius.

The following abbreviations are used (herein and in the examples):

BSA:	N,O-bis-(trimethylsilyl)-acetamide
BSS:	bis-(trimethylsilyl)-sulfate
BSTFA:	N,O-bis-(trimethylsilyl)-trifluoracetamide
BSU:	N,N'-bis(trimethylsilyl)-urea
Cefotaxime in free form:	7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-(acetyl-oxy)methyl-3-cephem-4-carboxylic acid
Ceftriaxone in free form:	7-[2-(Aminothiazol-4-yl)-2(Z)-(methoximino)acetamido]-3-{[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl}-3-cephem-4-carboxylic acid
Disodium ceftriaxone;	7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-{[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl}-3-cephem-4-carboxylic acid in the form of a disodium salt
HMDS:	1,1,1,3,3,3-hexamethyldisilazane
Sodium cefotaxime:	7-[2-(aminothiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-(acetyl-oxy)methyl-3-cephem-4-carboxylic acid in the form of a sodium salt
TMIS:	iodotrimethylsilane
TMSTf :	trimethylsilyl-trifluormethansulfonate

Example 1

7-[2-(Aminothiazol-4-yl)-2(Z)-methoximino)acetamido]-3-{[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-*as*-triazin-3-yl)thio]methyl}-3-cephem-4-carboxylic acid in the form of a disodium salt

Solution A

18.57 g of 7-amino-3-{[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-*as*-triazin-3-yl)thio]methyl}-3-cephem-4-carboxylic acid, suspended in 185 ml of dichloromethane, are treated under inert gas with 40.69 g of BSA while stirring the mixture at room temperature. The solution obtained is cooled to -10°.

Solution B

11.2 g of 4-bromo-2(Z)-methoximino-3-oxobutyric acid in 85 ml of dichloromethane, cooled to -10°, are treated under inert gas with10.41 g of phosphorpentachloride, added in portions, while stirring.

Solution C

3.81 g of thio urea, suspended in 50 ml of dichloromethane, are treated under inert gas with 40.7 g of BSA while stirring. A clear solution is obtained.

Solution B is added to solution A while stirring at ca. –10° under an inert gas atmosphere, the mixture obtained is cooled to ca. 0° and treated with solution C under inert gas. The reaction mixture obtained is stirred at ca. 0° and poured while stirring onto an ice-cooled solution of 41.5 g of sodium 2-ethylhexanoate in 250 ml of acetone/water. The mixture obtained is stirred in an ice bath and 250 ml of water and 500 ml of dchloromethane are added. The pH of the two-phase system obtained is adjusted with sodium bicarbonate solution to 6.5. A two-phase system is obtained. The organic phase is separated off and the pH of the aqueous phase is adjusted to 3 with 2 N HCl. Precipitation occurs. The precipitate obtained is filtrated off and suspended in 250 ml of acetone and 15 ml of water. The pH of the suspension obtained is adjusted to 6.5 by addition of 1 M aqueous sodium acetate. A clear solution is obtained and crystallization occurs. Acetone is added while stirring. The precipitate obtained is filtrated off and dried. Ceftriaxone in the form of a disodium salt and in the form of a hemiheptahydrate is obtained.

Example 2

7-[2-(Aminothiazol-4-yl)-2(Z)-methoximino)acetamido]-3-{[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-*as*-triazin-3-yl)thio]methyl}-3-cephem-4-carboxylic acid in the form of a disodium salt

Solutions A and B are produced as described in Example 1, but using in solution B 8.98 g of 4-chloro-2(Z)-methoximino-3-oxo-butyric acid instead of 11.2 g 4-bromo-2(Z)-methoximino-3-oxo-butyric acid. Solutions A and B are mixed and poured onto a suspension of 21.0 g of sodium bicarbonate in 340 ml of wate/2-propanol while stirring. The pH of the two-phase system obtained is adjusted with 2 N HCl to 2.0. The organic phase is separated off and treated with 8.25 ml of water, 4.45 g of triethylamine and 3.35 g of thiourea while stirring. Precipitation occurs. The precipitate is isolated, suspended in 250 ml of acetone and 15 ml of water and treated with 1 M aqueous sodium acetate in water. A clear solution is obtained and crystallization occurs. Acetone is added under stirring to the mixture obtained. Ceftriaxone in the form of a disodium salt and in the form of a hemiheptahydrate is obtained.

Example 3

7-[2-(Aminothiazol-4-yl)-2(Z)-methoximino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid

Solutions A and B are produced acording to a method as described in Example 2, but using in solution A 18.57 g of 7-aminocephalosporanic acid instead of 18.57 g of 7-amino-3-{[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-*as*-triazin-3-yl)thio]methyl}-3-cephem-4-carboxylic acid. While stirring the mixture obtained is poured onto an ice-cooled suspension of potassium bicarbonate in a mixture of water and 2-propanol. The pH of the two-phase system obtained is adjusted to 2.0 with 2 N HCl. The organic phase is separated off and treated with 7.5 ml of water and 3.81 g thiourea while stirring. The pH of the mixture is kept between 3.0 and 3.5 by addition of a solution of 2-amino-2,4,4-trimethylpentane in dichloromethane. A precipitate is obtained. 2-Propanol is added to the suspension obtained while stirring and the precipitate is isolated and dried.

7-[2-(Aminothiazol-4-yl)-2(Z)-methoximino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid is obtained.

Example 4

Ceftriaxone in free form

<u>Solution A</u>

23.87 g of sodium cefotaxim in 100 ml of dichloromethane are treated under inert gas with 19.31 g of BSTFA while stirring. To the mixture obtained 10.01 g of TMIS are added. The mixture otained is cooled to 0° and treated with further 20.02 g of TMIS while stirring.

Solution B

7.95 g of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin in 32 ml of dichloromethane are treated with 11.19 g of BSA. A clear solution is obtained.

Solution B is added to Solution A and the mixture obtained is stirred under inert gas. The mixture obtained is poured onto a mixture of 20.5 g of sodium acetate in 350 ml of water/methanol, the mixture obtained is treated with 6.20 g of sodium thiosulphate pentahydrate and 250 ml of water and 500 ml of dichloromethane are added. The pH of the two-phase system obtained is adjusted to 6.5 with sodium bicarbonate. The organic phase is separated off and the aqueous phase is treated with charcoal. From the mixture obtained the charcoal is filtrated off and the pH of the filtrate obtained is adjusted to 3.0 with 2N HCl. Ceftriaxone in free form precipitates and is filtrated off.

Examples 5 and 6

Ceftriaxone in free form

Are carried out according to the method as described in example 4; but using a Solution A (Example 5) and a Solution A (Example 6) as described below instead of a Solution A as described in Example 4. Ceftriaxone in free form is obtained.

Solution A (Example 5)

23.87 g of sodium cefotaxime in 100 ml of dichloromethane are treated with 8.88 g of HMDS while stirring under inert gas. The mixture obtained is treated at ca. 0° with 11.01 g of TMIS, and with further 20.01 g of TMIS.

Solution A (Example 6)

22.77 g of cefotaxim in free form in 100 ml of dichloromethane are treated with 19.37 g of HMDS while stirring under inert gas. The mixture obtained is treated at ca. 0° with 20.01 g of TMIS and is further stirred.

Example 7

Disodium ceftriaxone

Ceftriaxone sodium obtained according to example 5 in 2500 ml of methanol is stirred with charcoal. The charcoal is filtrated off and solvent from the filtrate obtained is evaporated off at 30-35°. To the evaporation residue obtained 500 ml of acetone and 100 ml of water are added. The pH of the mixture obtained is adjusted to 5.8 with 5 M aqueous sodium acetate. Crystallisation occurs and is completed by addition of acetone. The precipitate obtained is filtrated off, washed with acetone and dried. Crystalline disodium ceftriaxone in the form of a hemiheptahydrate in a purity of 99.4 % (HPLC, area) and a content of 83.7 % is obtained.

Reference Example

Disodium ceftriaxone without isolation of ceftriaxone in free form

Solution A and Solution B, produced according to Example 5, are reacted according to the description in Example 5 and worked up according to the description in Example 5; but omitting adjusting the pH of the aqueous solution obtained after filtrating off the charcoal and omitting isolation of ceftriaxone in free form according to Example 5. Instead, the aqueous solution obtained after filtrating off the charcoal according to the description in Example 5, is treated with 350 ml of acetone and the pH of the mixture obtained is adjusted to 5.8 with 5 M aqueous sodium acetate solution according to the description in example 7. The turbid solution obtained is seeded with disodium ceftriaxone obtained according to example 7. Crystallisation starts and is completed by addition of acetone according to the description 7. Crystalline dinatrium ceftriaxone is isolated and dried according to the description 7.
Crystalline disodium ceftriaxone in the form of a hemiheptahydrate in a purity of 98.1 % (HPLC, area) and a content of 52.6 % is obtained.

Example 8

Disodium ceftriaxone

Solution A

23.87 g of sodium cefotaxime in 100 ml of dichlormethane are treated with 30.31 g of BSS while stirring under inert gas in an ice-bath.

Solution B

7.95 g of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazine in 32 ml of dichloromethane are treated with 32.18 g of BSTFA while stirring and refluxing for several hours.

Solution B is added to solution A while stirring. The resulting mixture is treated under ice-cooling and inert gas with 38.90 g of TMSTf. The mixture obtained is poured into an ice-cooled solution of 20.5 g of sodium acetate in 350 ml of methanol/water and 250 ml of water and 500 ml of dichloromethane are added. The pH of the two-phase system obtained is adjusted with aqueous bicarbonate to 6.5. The organic phase is separated off and the aqueous phase is treated with charcoal. The charcoal is filtrated off and the pH of the filtrate obtained is adjusted to 3.0 with 2N HCl. A precipitate forms and the mixture is stirred in an ice-bath. The precipitate is filtrated off. The residue is dissolved in 3000 ml of methanol and treated with charcoal. The charcoal is filtrated off and solvent of the filtrate obtained is evaporated off at 30-35°. The evaporation residue obtained is treated with mit 300 ml of acetone and 150 ml of water adjusting the pH to ca. 5.8 with 5 M aqueous sodium acetate. To the mixture obtained 1500 of ml acetone are added and crystallisation occurs. The crystalline precipitate is filtrated off and dried.

Disodium ceftriaxone is obtained in a purity of 99.9% (HPLC, area).

Example 9

Disodium ceftriaxone – one pot procedure

23.87 g of cefotaxime in free form and 7.95 g of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin in 150 ml of dichloromethane are treated with 57.92 g of BSTFA while stirring under inert gas. A solution obtained is refluxed for several hours, cooled in an ice-bath, and treated with 33.34 g of TMSTf. The mixture obtained is poured onto an ice-cooled solution of 20.5 g of sodium acetate in 350 ml of methanol/water and 250 ml of water and 500 ml of dichloromethane are added. Further treatment and work-up is carried out according to the method described in example 8.

Disodium ceftriaxone is obtained in a purity of 99.6% (HPLC, area).

Example 10

Disodium ceftriaxone - one pot procedure

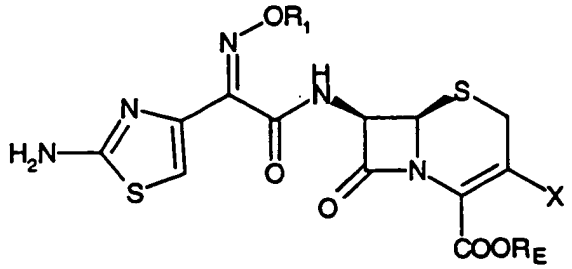
27.12 g of cefotaxime in free form and 8.12 g of 3-mercapto-2-methyl-(2,5-dihydro-6-hydroxy-5-oxo-as)-triazin in 100 ml of dichloromethane are refluxed under inert gas with 10.42 g of BSU. A precipitate obtained is filtrated off and the filtrate obtained is diluted with 100 ml of dichloromethane. 13.86 g of TMSTf are added to the mixture obtained under reflux. Under ice-cooling 5 g of ethanol and 7.5 g of triethylamine are added. A precipitate is obtained and is

filtrated off. The solid residue is dissolved in 100 ml of propylene glycol, treated with charcoal and filtrated. The pH of the filtrate obtained is adjusted to 5.2 with 5 N aqueous sodium acetate. Crystallization occurs while adding acetone.

Disodium ceftriaxone is obtained as a fine, crystalline precipitate in a purity of 98.2% (HPLC, area).

Patent Claims

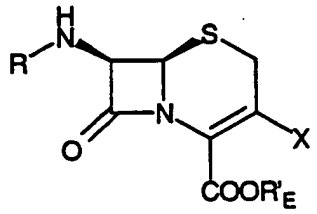
1. A process for the production of a compound of formula



I

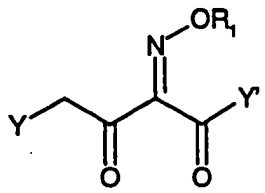
wherein X and R_1 are substituents useful in cephalosporin chemistry and R_E is hydrogen, a negative charge or together with the COO- group to which R_E is attached is an ester; comprising

i) reacting a compound of formula



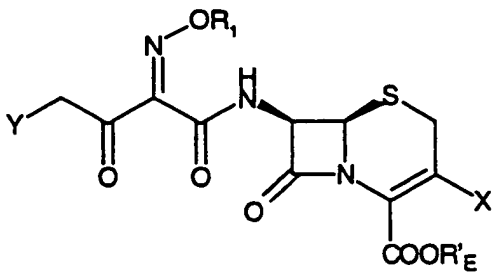
IV

wherein R is hydrogen or silyl, R'_E is silyl or together with the COO- group to which R_E is attached is an ester; and X is as defined above, with a compound of formula



III

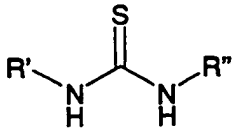
wherein Y is halogen, Y' is a group which forms a basis that a compound of formula III is in a reactive form; and R_1 is as defined above, to obtain a compound of formula



II

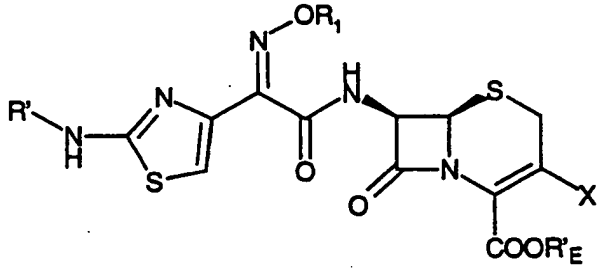
wherein Y, X, R'_E and R_1 are as defined above;

ii) reacting a compound of formula II wherein X, Y, R'_E and R_1 are as defined above, with a compound of formula



V

wherein R' is hydrogen or silyl and R" is silyl; to obtain a compound of formula



VI

wherein X, R_1, R' and R'_E are as defined above, and desilylating a compound of formula VI to obtain a compound of formula I; or

ii') desilylating a compound of formula II wherein Y, X, R'_E and R_1 are as defined above, and reacting a desilylated compound of formula II with thiourea in a solvent system containing organic solvent and water; to obtain a compound of formula I.

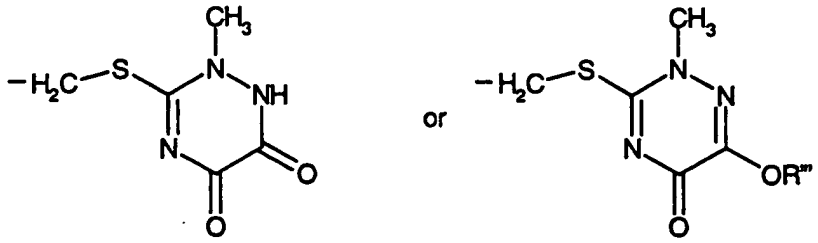
2. A process for the production of a compound of formula I, wherein X, R_1 and R_E are as defined in claim 1, comprising reacting a compound of formula II, wherein Y, X, R'_E and R_1 are as defined in claim 1, with a compound of formula V, wherein R' and R" are as defined in claim 1 according to step ii) as defined in claim 1; or

desilylating a compound of formula II, wherein Y, X, R'_E and R_1 are as defined in claim 1, and reacting a desilylated compound of formula II with thiourea according to step ii') as defined in claim 1, to obtain a compound of formula I.

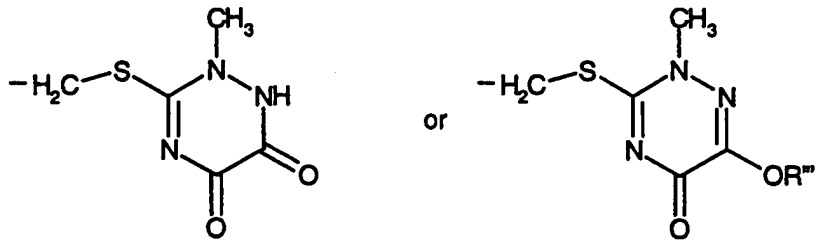
3. A process according to any one of claims 1 to 2 wherein a compound of formula I is ceftriaxone or cefotaxime.

4. A process according to any one of claims 1 to 3 wherein a compound of formula I is in the form of a solvate, or in the form of an ester or in the form of a salt; or in the form of an ester or in the form of a salt, and in the form of a solvate.

5. A process for the production of ceftriaxone in the form of a disodium salt comprising reacting a compound of formula II, wherein Y is as defined in claim 1, R_1 is CH_3, R'_E is silyl, and X is a group of formula



wherein R''' is silyl, with a compound of formula V, wherein R' and R'' are as defined in claim 1, to obtain a compound of formula VI, wherein R'_E is silyl; R_1 is CH_3, R' is as defined in claim 1 and X is a group of formula



wherein R''' is as defined above; and

i) reacting the reaction mixture obtained with water/organic solvent which is miscible with water and a base; and with water/organic solvent which is able to form a two-phase system with water;

ii) adjusting the pH of the mixture obtained to about 6.5;

iii) separating off the organic solvent from the two-phase system obtained;

iv) adjusting the pH of the aqueous phase obtained to a pH of about 3;

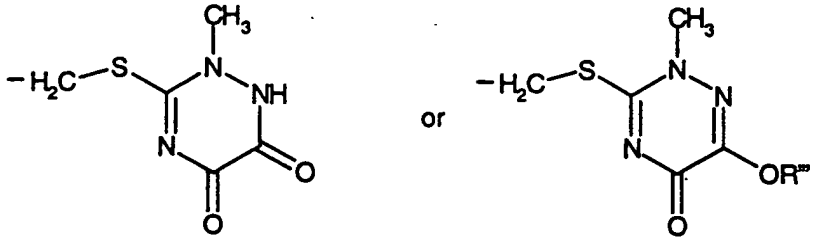
v) filtrating off the precipitate formed;

vi) suspending the precipitate obtained in a mixture of water and organic solvent which is miscible with water;

vii) adjusting the pH of the mixture obtained to about 6.5; and

viii) isolating ceftriaxone in the form of a disodium salt.

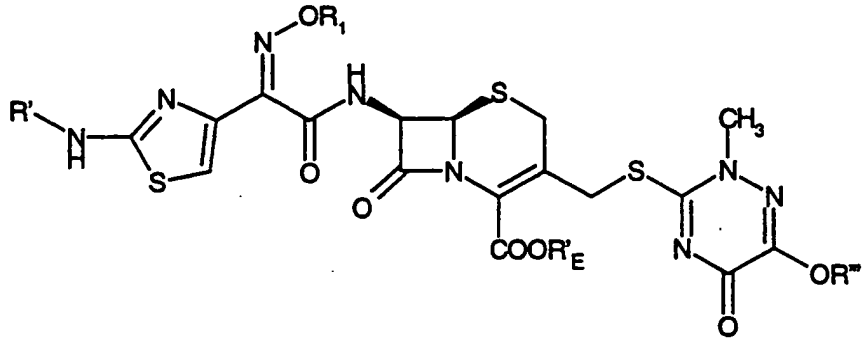
6. A compound of formula II as defined in claim 1, wherein R'_E, R_1 and Y are as defined in claim 1 and X denotes a group of formula



wherein R''' is silyl.

7. A compound of formula V as defined in claim 1, wherein R' is hydrogen or tri(C_{1-4})alkylsilyl, and R'' is tri(C_{1-4})alkylsilyl.

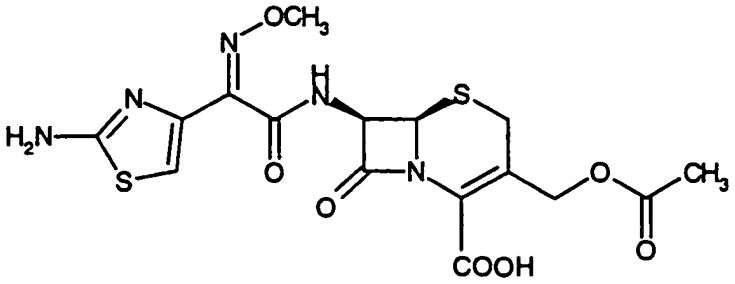
8. A compound of formula



wherein R_1 is as defined in claim 1 and R', R'_E and R''' are tri(C_{1-4})alkylsilyl.

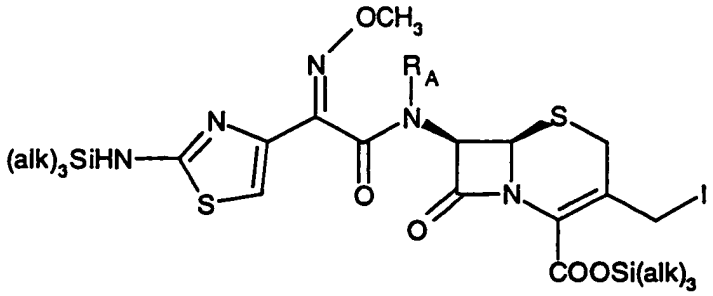
9. A process for the production of ceftriaxone in the form of a disodium salt comprising

i) silylating a compound of formula



IIA

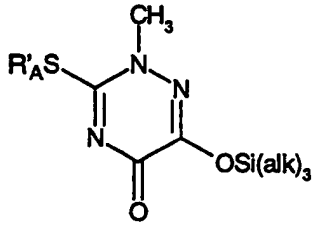
or a compound of formula IIA in the form of a salt and iodinating; to obtain a compound of formula



IIIA

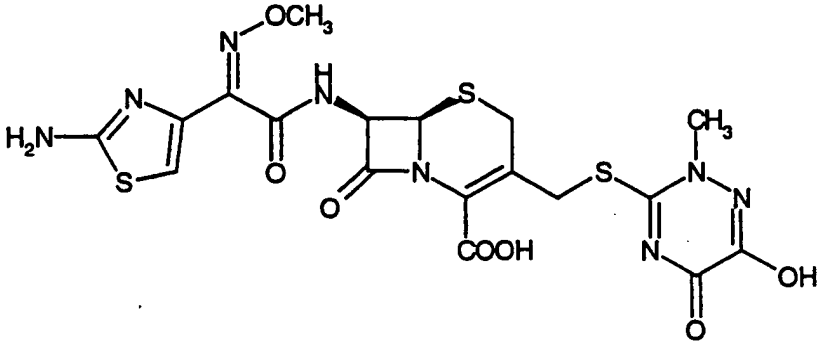
wherein R_A is hydrogen or trialkylsilyl and alk is alkyl,

ii) reacting a compound of formula IIIA obtained in step i) with a compound of formula



IVA

wherein R'_A is hydrogen or trialkylsilyl, e.g. trimethylsilyl; and desilylating, to obtain a compound of formula

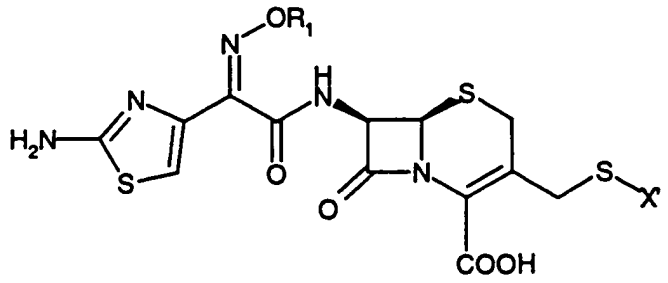


VA

iii) isolating a compound of formula VA obtained in step ii) from the reaction mixture; and

iv) converting a compound of formula VA obtained in step iii) into ceftriaxone in the form of a disodium salt.

10. A process for the production of a compound of formula

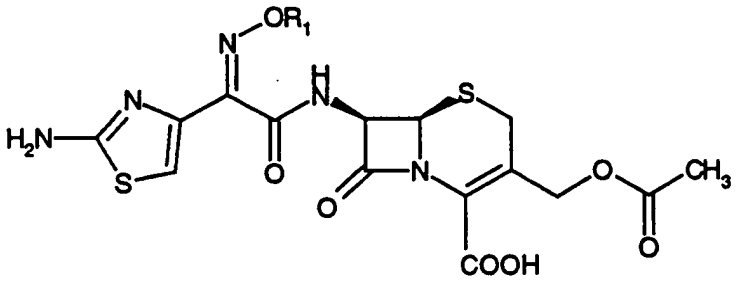


IB

wherein X' and R_1 are substituents useful in cephalosporin chemistry;

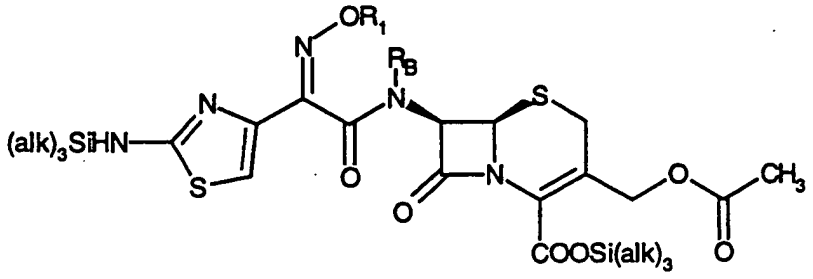
comprising

i) silylating a compound of formula



IIB

or a compound of formula IIB in the form of a salt, wherein R_1 is as defined above, to obtain a compound of formula



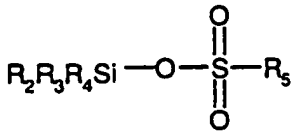
IIIB

wherein R_B is hydrogen or trialkylsilyl, and alk is alkyl;

ii) reacting a compound of formula IIIB with a compound of formula

R'_BS-X' IVB

wherein R'_B is hydrogen or trialkylsilyl and X' is as defined above, in the presence of a compound of formula



VB

wherein R_2, R_3 and R_4 independently of each another are aryl or alkyl, and R_5 is alkyl or aryl; and

iii) isolating a compound of formula IB from the reaction mixture obtained in step ii).

11. A process according to claim 10 wherein in step ii) a compound of formula VB is trimethylsilyl-trifluoromethanesulfonate.

12. A process according to an one of claims 10 to 11, wherein ceftriaxone is produced.

13. A process according to anyone of claims 10 to 12, wherein a compound of formula IB is obtained in the form of a solvate, or in the form of an ester or in the form of a salt; or in the form of an ester or in the form of a salt and in the form solvate.

14, A process according to any one of claims 10 to 13, wherein ceftriaxone in free form is isolated from the reaction mixture and is converted into ceftriaxone in the form of a disodium salt; e.g. and in the form of a hemiheptahydrate.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 00/03428

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/06 C07F7/10 C07F7/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 842 937 A (HICHEM PHARMA S P A ;S B D S R L (IT)) 20 May 1998 (1998-05-20) the whole document	1-14
Y	EP 0 791 596 A (LUPIN LAB LTD) 27 August 1997 (1997-08-27) the whole document	1-14
A	EP 0 556 768 A (BIOCHEMIE GMBH) 25 August 1993 (1993-08-25) the whole document	1-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2000	26/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Interna al Application No
PCT/EP 00/03428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 123, no. 5, 31 July 1995 (1995-07-31) Columbus, Ohio, US; abstract no. 55587, WINIARSKI J. ET AL: "Method of preparing ceftriaxone" XP002142191 abstract & PL 163 399 A (POLSKA AKADEMIA) 31 March 1994 (1994-03-31)	1-14
X	W. WALTER ET AL: "N-(Trimethylsilyl)thioharnstoffe" LIEBIGS ANNALEN DER CHEMIE., no. 2, 1979, pages 263-277, XP002142189 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0170-2041 the whole document	7
X	M. GRUBER ET AL.: "Eine neue Bildungsweise der Phosphor-Phosphor-Bindung." CHEMISCHE BERICHTE - INORGANIC AND ORGANOMETALLIC CHEMISTRY - A EUROPEAN JOURNAL., vol. 123, no. 6, 1990, pages 1313-1317, XP002142190 VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM., DE ISSN: 0009-2940 the whole document	7

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/EP 00/03428

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0842937 A	20-05-1998	IT MI962406 A	19-05-1998
EP 0791596 A	27-08-1997	EP 0791597 A	27-08-1997
EP 0556768 A	25-08-1993	AT 399877 B	25-08-1995
		AT 30992 A	15-12-1994
		AT 172734 T	15-11-1998
		DE 69321749 D	03-12-1998
		DE 69321749 T	22-04-1999
		ES 2124748 T	16-02-1999
		JP 2609039 B	14-05-1997
		JP 6009648 A	18-01-1994
		SG 47054 A	20-03-1998
		US 5574155 A	12-11-1996
PL 163399 A	31-03-1994	NONE	

US 20030199712A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2003/0199712 A1

Deshpande et al. (43) Pub. Date: Oct. 23, 2003

(54) PROCESS FOR THE PREPARATION OF CEPHALOSPORIN INTERMEDIATE AND ITS USE FOR THE MANUFACTURE OF CEPHALOSPORIN COMPOUNDS

(75) Inventors: **Pandurang Bulwant Deshpande**, Maharashtra (IN); **Parven Kumar Luthra**, Chennai (IN); **Pratik Ramesh Sathe**, Chennai (IN); **Sivakumaran Sundaravadivelan**, Kanchipuram (IN); **Praveen Nagesh Ganesh**, Chennai (IN)

Correspondence Address:
OLIFF & BERRIDGE, PLC
P.O. BOX 19928
ALEXANDRIA, VA 22320 (US)

(73) Assignee: **Orchid Chemicals and Pharmaceuticals Limited**, Tamilnadu (IN)

(21) Appl. No.: **10/245,490**

(22) Filed: **Sep. 18, 2002**

(30) **Foreign Application Priority Data**

Apr. 19, 2002 (IN)..... 305/MAS/2002

Publication Classification

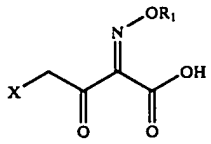
(51) **Int. Cl.**[7] **C07C 249/12**

(52) **U.S. Cl.** **562/560**; 204/157.84

(57) ABSTRACT

The present invention relates to a process for the preparation of 4-halogeno-2-substitutedimino-3-oxo-butyric acid of formula (I)

(I)

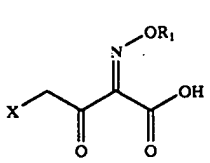


wherein R_1 represents CH_3, $CR^aR^bCOOR^c$ where R^a and R^b independently represent hydrogen or methyl and R^c represents hydrogen or (C_1-C_6)alkyl, X represents halogen such as chlorine or bromine, also discloses the activation of this acid and its further use in the preparation of cephalosporanic antibiotics (II) in excellent yields and purity

PROCESS FOR THE PREPARATION OF CEPHALOSPORIN INTERMEDIATE AND ITS USE FOR THE MANUFACTURE OF CEPHALOSPORIN COMPOUNDS

FIELD OF INVENTION

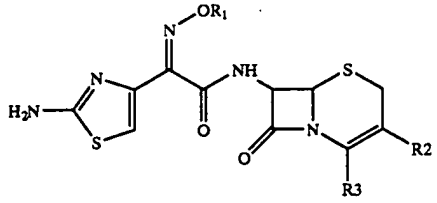
[0001] The present invention relates to a process for the preparation of 4-halogeno-2-substituted imino-3-oxo-butyric acid of general formula (I)



(I)

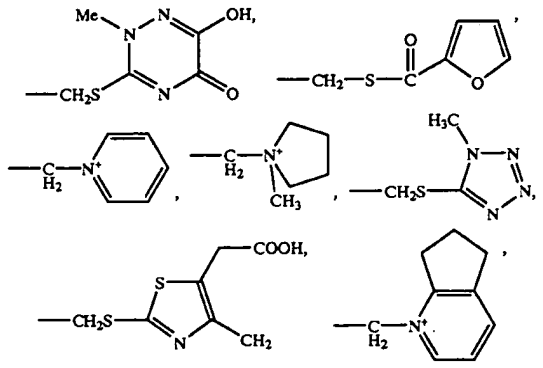
[0002] wherein R_1 represents CH_3, $CR^aR^bCOOR^c$ where R^a and R^b independently represent hydrogen or methyl and R^c represents hydrogen or $(C_1$-$C_6)$alkyl; X represents halogen such as chlorine or bromine.

[0003] The invention also discloses the activation of this acid and its further use in the preparation of cephalosporin antibiotic of formula (II) or its solvates in excellent yields and purity.

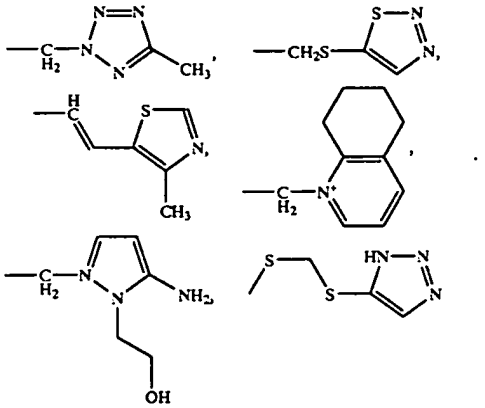


(II)

[0004] wherein R_1 represents CH_3, $CR^aR^bCOOR^c$ where R^a and R^b independently represent hydrogen or methyl and R^c represents hydrogen or $(C_1$-$C_6)$alkyl; R_2 represents H, CH_3, CH_2OCH_3, CH_2OCOCH_3, $CH{=}CH_2$,



-continued



[0005] R_3 is carboxylate ion or $COOR^d$, where R^d represents hydrogen, esters which form a prodrug or a counter ion which forms a salt.

BACKGROUND OF THE INVENTION

[0006] U.S. Pat. No. 5,095,149 describes a process for the preparation of 4-halogeno-2-methoxyimino-3-oxo-butyric acid of formula (I) by brominating the methoxy imino compound of general formula (III) by bromine in mixture of IPE and ethylene di chloride. Ethylene dichloride is a toxic solvent and hence its use in the preparation of pharmaceuticals has to be avoided.

[0007] U.S. Pat. No. 5,109,131 describes a process for the preparation of 4-halogeno-2-methoxyimino-3-oxo-butyric acid of formula (I) starting with the reaction of diketene and, tert-butyl alcohol, followed by oximation, methylation, hydrolysis and halogenation. This method involves the hydrolysis and halogenation in two steps.

[0008] Synthesis of 4-halogeno-2-methoxyimino-3-oxo-butyric acid is reported in patent no. EP 0 030 294 and a large number of references are available in the patent literature disclosing the use of 4-halogeno-2-substituted imino-3-oxo-butyric acid represented by formula (I) as the starting material. EP 0030294 discloses the condensation of the 4-halogeno-2-substituted imino-3-oxo-butyric acid represented by formula (I) with cephem carboxylic acids by using PCl_5. Another EP patent 0 842 937 discloses the formation of amide bond with cephem moiety by reacting with the thioester derivative of 4-chloro-2-methoxyimino-3-oxo-butyric acid. The thioester was prepared by reacting 4-chloro-2-methoxyimino-3-oxo-butyric acid with 2,2'-dithio-bis-benzothiazole in the presence of triphenyl phosphine which is a costly material and its by product triphenyl phosphine oxide is also difficult to remove from the reaction mixture.

OBJECTIVES OF THE INVENTION

[0009] The primary objective of the invention is to provide a new process for the preparation of 4-halogeno-2-substituted imino-3-oxo-butyric acid of the general formula (I), which would be suitable for being used in the manufacture of cephalosporin antibiotic, which would be easy to implement in commercial scales.

[0010] Another objective of the present invention is to provide a process for the preparation of 4-halogeno-2-substituted imino-3-oxo-butyric acid of the general formula (I), in good yields with high purity.

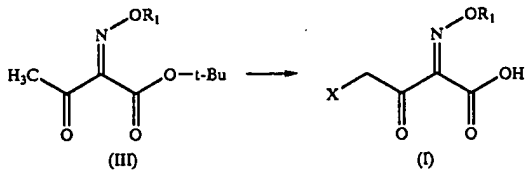
[0011] Another objective of the present invention is to carry out the halogenation by photochemical irradiation which would give higher yield and halogenation can also be achieved in presence or absence of solvents thus making the process more environmental friendly.

[0012] Another objective of the present invention is to provide a process for the preparation of cephalosporin antibiotics e.g. cefotaxime, ceftriaxone, cefetamet, ceftiofur, cefditoren, cefpodoxime, ceftadizime, cefepime, cefixime, cefinenoxime, cefodizime, cefoselis, cefquinome, cefpirome, cefteram, cefuzonam etc. which comprises use of 4-halogeno-2-substituted imino-3-oxo-butyric acid of the general formula (I), prepared by the process of the present invention.

SUMMARY OF THE INVENTION

[0013] Accordingly, the present invention provides a process for the preparation of 4-halogeno-2-substituted imino-3-oxo-butyric acid of formula (I), which comprises hydrolysis and halogenation of the ester of formula (III) by photochemical irradiation in one pot using a halogenating agent in the absence or presence of a solvent at a temperature in the range of -20° C. to 30° C. The reaction is as shown in the Scheme-1 below:

Scheme-1

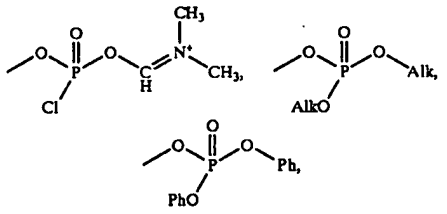


[0014] wherein R_1 represents CH_3, $CR^aR^bCOOR^c$ where R^a and R^b independently represent hydrogen or methyl and R^c represents hydrogen or $(C_1$-$C_6)$alkyl; X represents halogen such as chlorine or bromine.

DETAILED DESCRIPTION OF THE INVENTION

[0015] In an embodiment of the present invention relates to a process for the condensation of the acid of formula (I) thus produced with different 7-amino cephem derivatives of formula (V), which comprises:

[0016] (i) activation of the 4-halogeno-2-substitutedimino-3-oxo-butyric acid of general formula (I), using conventional activation agents at a temperature in the range of -50° C. to 10° C. to produce a compound formula (IV) where R_1 and X are as defined above and X' represents halogen such as chlorine, bromine or activating groups such as



[0017] where Alk group represents $(C_1$-$C_4)$alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or iso-butyl.

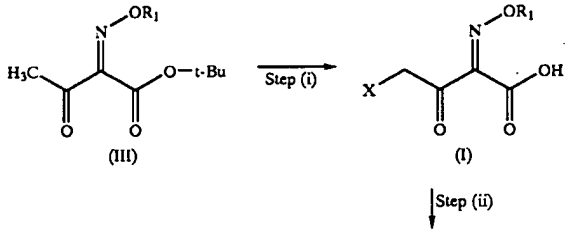
[0018] (iii) condensing the activated compound of formula (IV) with 7-amino cephem derivatives of formula (V) where R_4 is hydrogen or trimethylsilyl, R_2 and R_3 are as defined earlier, in the presence of a solvent at a temperature in the range of -50° C. to 10° C. to produce an active compound of formula (VI) where all symbols are as defined earlier,

[0019] (iv) cyclising the compound of formula (VI) with thiourea in the presence of water miscible solvents to produce cephalosporin antibiotic of formula (II), where all symbols are as defined earlier, and

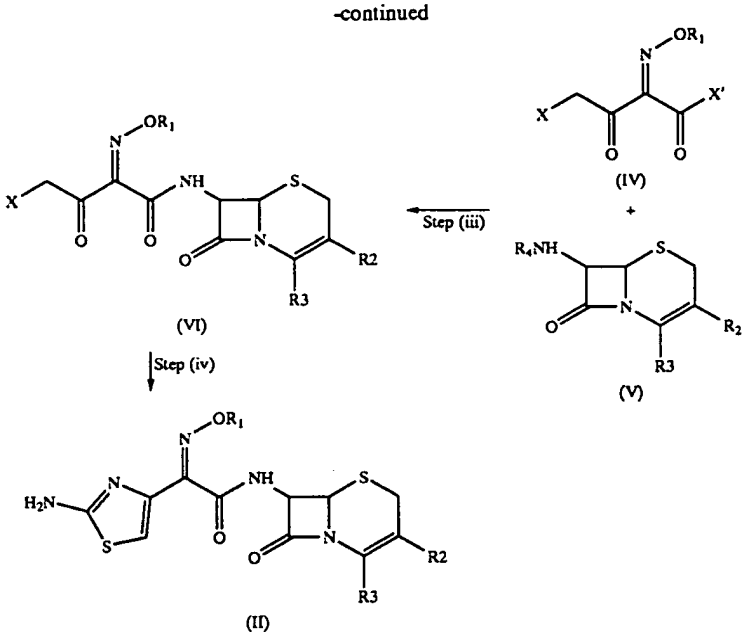
[0020] (v) optionally converting the compound of formula (II) to its pharmaceutically acceptable esters, salts or solvates.

[0021] The process is as shown in scheme-2 below:

Scheme-2



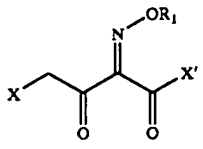
-continued



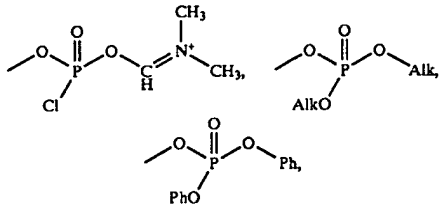
[0022] Another embodiment of the present invention, the compound of formula (VI) can be cyclised with the thiourea without isolating the condensed product.

[0023] In yet another embodiment of the present invention there is provided a novel intermediate of formula (IV)

(IV)



[0024] wherein X represents halogen such as chlorine or bromine, R_1 represents CH_3, $CR^aR^bCOOR^c$ where R^a and R^b independently represent hydrogen or methyl and R^c represents hydrogen or $(C_1$-$C_6)$alkyl and X' represents an activating group such as



[0025] where Alk group represents $(C_1$-$C_4)$alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or isobutyl.

[0026] In another embodiment of the present invention, the solvent used in step (i) is selected from diisopropyl ether, dichloromethane, acetic acid and mixtures thereof. The halogenating agent used is chlorine or bromine.

[0027] In yet another embodiment of the present invention, provides a process to perform bromination by photochemical irradiation in the absence or presence of a solvent.

[0028] In yet another embodiment of the present invention, the light source used for photochemical halogenation is IR or UV radiation, preferably UV radiation.

[0029] In still another embodiment of the present invention, the activation in step (ii) is carried out using PCl_5, $DMF/POCl_3$, oxalyl chloride, $SOCl_2/DMF$, diphenylchlorophosphoridate, dialkyl chlorophosphoridate, in the presence of a solvent selected from halogenated alkanes, ethyl acetate, tetrahydrofuran, aromatic hydrocarbons, acetone, acetonitrile, dialkylethers or mixtures thereof.

[0030] In yet another embodiment of the present invention condensation in step (iii) is carried out in the presence of a solvent selected from halogenated alkanes, ethyl acetate, tetrahydrofuran, aromatic hydrocarbons, acetone, acetonitrile, dialkylethers or mixtures thereof.

[0031] In yet another embodiment of the present invention the cyclisation in step (iv) is carried out using a mixture of water and organic solvent selected from tetrahydrofuran, acetone, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane, $(C_1$-$C_3)$ alcohol or mixtures thereof, in the presence of sodium acetate.

[0032] In still another embodiment of the present invention the counter ion represented by R^d is alkali metal, preferably sodium.

[0033] In still another embodiment of the present invention the prodrug ester represented by R^d is —(CH_2)—O—

$C(=O)—C(CH_3)_3$, $—CH(CH_3)—O—C(=O)—CH_3$ or $—CH(CH_3)—O—C(=O)—O—CH(CH_3)_2$.

[0034] In another embodiment of the present invention the compound of formula (I) obtained is a syn-isomer.

[0035] In another embodiment of the present invention, the compound of formula (V), when R_4 represents trimethylsilyl, the silylation is carried out by using silylating agent selected from N,O-bis-(trimethylsilyl)acetamide(BSA), hexamethyldisilazane (HMDS) trimethylchlorosilane (TMCS), dichlorodimethylsilane.

[0036] Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure. However, since the major characteristic feature of the present invention resides in the preparation of 4-halogeno-2-substituted imino-3-oxo-butyric acid of general formula (I) in preparing the cephalosporin antibiotics, the technical scope of the present invention should not be limited to the following examples.

[0037] The following examples are provided by way of illustration only and should not be limited to construe the scope of the invention

EXAMPLE-1

[0038] Preparation of 4-chloro-2-methoxyimino-3-oxobutyric Acid Using Photochemical Irradiation

[0039] In di-isopropyl ether (250 ml), tert-butyl 2-methoxyimino-3-oxobutyrate (100 gm) was dissolved and chlorine gas was introduced into the solution at 0-5° C. in the presence of ultraviolet radiation over a period of 18 hours. After completion of the introduction, water (150 ml) was added and then stirred to conduct the water washing to remove the inorganic by-products.

[0040] Subsequently the organic layer was dried over anhydrous magnesium sulphate, after which the solvent was distilled off under reduced pressure. To the residual was added xylene (100 ml), cooled to (−5 to −10° C.) to get the white crystals of 4-chloro-2-methoxyimino-3-oxobutyric acid. (Purity: 96-98%)

EXAMPLE-2

[0041] Preparation of 4-chloro-2-methoxyimino-3-oxobutyric Acid Using Photochemical Irradiation

[0042] t-Butyl 2-methoxyimino-3-oxobutyrate (100 g) was taken in the reactor and chlorine gas was introduced into the solution at 10°-20° C. in the presence of ultraviolet radiation over a period of 18 hours. After completion of the introduction, water (150 ml) was added and then stirred to conduct the water washing to remove the inorganic by-products.

[0043] Subsequently the product was dried over anhydrous magnesium sulphate and decanted. Vacuum was applied to pull out traces of acidic vapors. To the residue was added xylene (100 ml), cooled to (−5 to −10° C.) to get the white crystals of 4-chloro-2-methoxyimino-3-oxobutyric acid. (Purity: 96-98%)

EXAMPLE-3

[0044] Preparation of 7-[[(Z)-2-(aminothiazol-4-yl)-2-methoxyimino]acetamido]-3-(furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic Acid Sodium (Ceftiofur Sodium).

Step-I

[0045] Silylation of 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic Acid:

[0046] Methylene dichloride (100 ml) was charged to the reaction flask followed by addition of 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid (10.0 g) and stirred at room temperature. N, O-bis-(trimethylsilyl)acetamide (BSA) (18.0 g) was added drop wise at room temperature and continued stirring for 2-3 hrs at the same temperature.

Step-II

[0047] Activation of 4-chloro-2-methoxyimino-3-oxobutyric Acid with PCl_5

[0048] Methylene dichloride (60 ml) was charged in the flask followed by addition of 4-chloro-2-methoxyimino-3-oxo-butyric acid (6.3 g) obtained in example 1 or 2 and stirred at −40° C. PCl_5 (7.3 g) was added portion wise at 40° C. and continued stirring for 1 hr at the same temperature.

Step-III

[0049] Condensation of Activated 4-chloro-2-methoxyimino-3-oxobutyric Acid and Silylated 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic Acid

[0050] Silylated 7-amino-3-[(2-furanylcarbonyl)thiomethyl)-3-cephem-4-carboxylic acid obtained in step (I) above, at −40° C. was transferred to the activated 4-chloro-2-methoxyimino-3-oxobutyric acid obtained in step (II) above, in one lot. The temperature of the reaction mass was maintained at −40° C. for 30 min. The progress of the reaction was monitored by HPLC. After completion of the reaction, water (100 ml) was added, stirred at room temperature for another 30 min. The precipitated product was filtered and washed with water to give the condensed product (Purity 99.0%).

Step (IV)

[0051] Cyclisation with Thiourea

[0052] Tetrahydrofuran (150 ml) and water (75 ml) were charged into the reaction flask followed by the addition of condensed product (15.0 g) obtained in step (III) above, thiourea(2.7 g) and sodium acetate (8.0 g). Stirred the reaction mixture at room temperature for 3 hrs. The progress of the reaction was monitored by HPLC. After completion of reaction, sodium chloride (145.0 g) was added to the reaction mixture and stirred at room temperature for 30 min. The tetrahydrofuran layer was separated and was added THF (240 ml), charcoal (5.0 g) stirred for 1 hr at room temperature. To the THF layer $MgSO_4$ (15.0 g) was added to remove the traces of water, decanted the THF layer, to which sodium-2-ethyl hexanoate (9.4 g, 168 mw) in THF (50 ml) was added. Precipitation of the product started after 1 hr of stirring. The precipitated ceftiofur sodium was filtered and washed with acetone (11.0 g, Purity 99.0%).

EXAMPLE-4

[0053] Preparation of 7-[[(Z)-2-(aminothiazol-4-yl)-2-methoxyimino]acetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-carboxylic Acid Sodium (Ceftriaxone Sodium).

Step-I

[0054] Silylation of 7-amino-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-carboxylic Acid:

[0055] Methylene dichloride (70 ml) was charged to the reaction flask followed by addition of 7-amino-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl) thio methyl]-3-cephem-4-carboxylic acid (5.0 g, 1.0 mol) and stirred at room temperature. N, O-bis-(trimethylsilyl)acetamide (BSA) (9.0 g, 3.3 mol) was added drop wise at room temperature and continued stirring for 2-3 hrs at the same temperature. The mixture was then cooled to -30° C.

Step-II

[0056] Activation of 4-chloro-2-methoxyimino-3-oxo-butyric Acid with PCl_5

[0057] Methylene dichloride (20 ml) was charged in the flask followed by addition of 4-chloro-2-methoxyimino-3-oxo-butyric acid (2.6 g, 1.1 mol) obtained in example 1 or 2 and stirred at -30° C. PCl_5 (3.3 g, 1.1 mol) was added portion wise at -30° C. and continued stirring for 1 hr at the same temperature.

Step-III

[0058] Condensation of activated 4-chloro-2-methoxyimino-3-oxo-butyric Acid and Silylated 7-amino-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl) thiomethyl]-3-cephem-4-carboxylic Acid

[0059] Silylated 7-amino-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio methyl]-3-cephem-4-carboxylic acid obtained in step (I) above, at -30° C. was transferred to the activated 4-chloro-2-methoxyimino-3-oxobutyric acid obtained in step (II) above, in one lot. The temperature of the reaction mass was maintained at -30° C. for 30 min. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was poured into chilled DM water (200 ml), stirred at room temperature for another 1 hour. The precipitated product was filtered and washed with water to give the condensed product (Purity 99.0%).

Step (IV)

[0060] Cyclisation with Thiourea

[0061] To a mixture of 50 ml THF and 50 ml DM water was added the condensed compound (10.0 gm, 1.0 mol) obtained in step (III) above, followed by thiourea (2.85 gm, 2.0 mol) and sodium acetate (7.7 gm, 5.0 mol). The reaction was stirred for 1.0 hour at room temperature. After completion of reaction, the mixture was cooled to 0° C. and adjusted to pH 3.0 with 1:1 HCl. The precipitated solid was filtered, washed with DM water and the wet solid was charged into a mixture of acetone (300 ml) and DM water (30 ml). The reaction mass was cooled to 0° C. and pH adjusted to 6.8 with saturated sodium acetate and stirred for 30 minutes. The precipitated solid was filtered, washed with 2x30 ml chilled acetone and dried under nitrogen to yield Ceftriaxone sodium salt.(Purity: 99%).

EXAMPLE-5

[0062] Preparation of 7-[[(Z)-2-(aminothiazol-4-yl)-2-methoxyimino]acetamido]-3-acetoxymethyl]-3-cephem-4-carboxylic Acid (Cefotaxime).

Step-I

[0063] Silylation of 7-amino-3-acetoxymethyl-3-cephem-4-carboxylic Acid:

[0064] Methylene dichloride (140 ml) was charged to the reaction flask followed by addition of 7-amino-3-acetoxymethyl-3-cephem-4-carboxylic acid (10.0 gm, 1.0 mol) and stirred at room temperature. N, O-bis-(trimethylsilyl)acetamide (BSA) (24.6 g, 3.3 mol) was added drop wise at room temperature and continued stirring for 3 hrs at the same temperature to get a clear solution. The mixture was cooled to -30° C.

Step-II

[0065] Activation of 4-chloro-2-methoxyimino-3-oxobutyric acid with PCl_5

[0066] Methylene dichloride (30 ml) was charged in the flask followed by addition of 4-chloro-2-methoxyimino-3-oxo-butyric acid (7.2 gm, 1.1 mol) obtained in example 1 or 2 and stirred at -30° C. PCl_5 (9.3 gm, 1.1 mol) was added portion wise at -30° C. and continued stirring for 1 hr at the same temperature.

Step-III

[0067] Condensation of activated 4-chloro-2-methoxyimino-3-oxobutyric Acid and Silylated 7-amino-3-acetoxymethyl-3-cephem-4-carboxylic Acid

[0068] Silylated 7-amino-3-acetoxymethyl-3-cephem-4-carboxylic acid obtained in step (I) above at -30° C. was transferred to the activated 4-chloro-2-methoxyimino-3-oxobutyric acid obtained in step (II) above in one lot. The temperature of the reaction mass was maintained at -30° C. for 30 min. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was poured into 200 ml chilled DM water and stirred for 1 hour at 25° C. The precipitated solid was filtered; washed with DM water until washings are neutral and dried to get the open chain condensed product. (Purity 99. 0%).

Step (IV)

[0069] Cyclisation with Thiourea

[0070] Tetrahydrofuran (50 ml) and water (50 ml) were charged into the reaction flask followed by the addition of condensed product (10.0 gm, 1.0 mol) obtained in step (III) above, thiourea(3.5 gin, 2.0 mol) and sodium acetate (15.7 gm, 5.0 mol). Stirred the reaction mixture at room temperature for 1 hr. The progress of the reaction was monitored by HPLC. After completion of reaction, the mixture was cooled to 10° C. and pH adjusted to 2.5 with 1:1 HCl. The mixture was stirred for 1 hour to complete precipitation. The precipitated solid was filtered, washed well with DM water until washings are neutral and dried under vacuum at 35° C. to yield Cefotaxime acid. (Purity: 92%).

EXAMPLE 6

[0071] Preparation of 7-[[(Z)-2-(aminothiazol-4-yl)-2-methoxyimino]acetamido]-3-(furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic Acid Sodium (Ceftiofur Sodium).

Step-I

[0072] Silylation of 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic Acid:

[0073] To a solution of 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid (6.8 gm, 1.2 mol) in ethyl acetate(68 ml), bis-silylated acetamide (BSA) (16.6 gm, 4.0 mol) was added drop wise at room temperature and continued stirring for 2-3 hrs at the same temperature.

Step (II)

[0074] Activation of 4-chloro-2-methoxyimino-3-oxobutyric Acid with DMF/$POCl_3$

[0075] To a suspension of vilsmeir reagent prepared from $POCl_3$ (3.58 gm, 1.4 mol) and DMF (1.71 gm, 1.4 mol) in acetonitrile (24 ml) was added 4-chloro-2-methoxyimino-3-oxo butyric acid (3.0 gm, 1.0 mol) obtained in example 1 or 2 under ice-cooling at 0-5° C. The mixture was stirred at the same temperature for 30 minutes.

Step-III

[0076] Condensation of activated 4-chloro-2-methoxyimino-3-oxobutyric acid and silylated 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid Silylated 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid obtained in step (I) above, was added to the activated acid solution obtained in step (II) above at −25° C. After being stirred at −28° C.−−10° C. for 1 hour, add ice-water (25 ml). The separated organic layer was washed with water (75 ml). The organic solution was dried and condensed under reduced pressure to give 5.0 gm of the required product.

Step (IV)

[0077] Cyclisation with Thiourea

[0078] Tetrahydrofuran (50 ml) and water (25 ml) were charged into the reaction flask followed by the addition of condensed product (5.0 gm) obtained in step (III) above, thiourea(0.9 gm) and sodium acetate (2.8 gm). Stirred the reaction mixture at room temperature for 3 hrs. The progress of the reaction was monitored by HPLC. After completion of reaction, sodium chloride (48.0 gm) was added to the reaction mixture and stirred at room temperature for 30 min. The tetrahydrofuran layer was separated and was added THF (80 ml), charcoal (0.5 gm) stirred for 1 hr at room temperature. To the THF layer $MgSO_4$ (5.0 gm) was added to remove the traces of water, decanted the THF layer, to which sodium-2-ethyl hexanoate (3.1 gm) in THF (20 ml) was added. Precipitation of the product started after 1 hr of stirring. The precipitated Ceftiofur sodium was filtered and washed with acetone (3.2 gm, Purity 98.0%).

EXAMPLE-7

[0079] Preparation of 7-[[(Z)-2-(aminothiazol-4-yl)-2-methoxyimino]acetamido]-3-(furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic Acid Sodium (Ceftiofur Sodium).

Step (I)

[0080] Synthesis of diethyl-(4-chloro-2-methoxyimino-3-oxabutrate) Phosphoridate

[0081] 4-chloro-2-methoxyimino-3-oxobutyric acid (3.0 gm) obtained in example 1 or 2 was suspended in dichloromethane (24 ml). Triethylamine (0.90 gm) was added into this solution and then diethylchlorophosphoridate (24.52 gm):was also added thereto over 20 minutes while maintaining the solution under nitrogen atmosphere at 0° C. to 5° C. The mixture was stirred for 2 hours. After the reaction was completed, distilled water (25 ml) was added to the reaction solution and the mixture was stirred for 5 minutes. The organic layer was separated, washed successively with 5% aqueous sodium bicarbonate solution (25 ml) and saturated saline (25 ml), dried over magnesium sulfate, filtered and then concentrated under reduced pressure to obtain 5.9 gm of the title compound.

Step-II

[0082] Silylation of 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic Acid:

[0083] To a solution of 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid (6.8 gm, 1.2 mol) in ethyl acetate(68 ml) N,O-bis-(trimethylsilyl)acetamide.(BSA) (16.6 gm, 4.0 mol) was added drop wise at room temperature and continued stirring for 2-3 hrs at the same temperature.

Step-III

[0084] Condensation of Diethyl-(4-chloro-2-methoxyimino-3-oxabutrate) Phosphoridate and Silylated 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic Acid

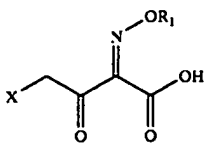
[0085] The suspension of the activated reagent obtained in step (I) above was added to the silylated 7-amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid obtained in step (II) above at −25° C. After stirring for 1 hour at −30° C. to −10° C., ice-water (25 ml) was added. The separated organic layer was washed with water (75 ml). The organic solution was dried and condensed under reduced pressure to give 7.5 gm of the required product.

Step (IV)

[0086] Cyclisation with Thiourea

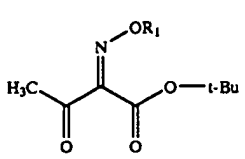
[0087] Tetrahydrofuran (50 ml) and water (25 ml) were charged into the reaction flask followed by the addition of condensed product (5.0 gm) obtained in step (III) above, thiourea (0.9 gm) and sodium acetate (2.8 gm). Stirred the reaction mixture at room temperature for 3 hrs. The progress of the reaction was monitored by HPLC. After completion of reaction, sodium chloride (48.0 gm) was added to the reaction mixture and stirred at room temperature for 30 min. The tetrahydrofuran layer was separated and was added THF (80 ml), charcoal (0.5 gm) stirred for 1 hr at room temperature. To the THF layer $MgSO_4$ (5.0 gm) was added to remove the traces of water, decanted the THF layer, to which sodium-2-ethyl hexanoate (3.1 gm) in THF (20 ml) was added. Precipitation of the product started after 1 hr of stirring. The precipitated Ceftiofur sodium was filtered and washed with acetone (3.0-3.2 gm, Purity 98.0%).

1. A process for the preparation of 4-halogeno-2-substituted imino-3-oxo-butyric acid of formula (I)



(I)

wherein R_1 represents CH_3, $CR^aR^bCOOR^c$ where R^a and R^b independently represent hydrogen or methyl and R^c represents hydrogen or $(C_1$-$C_6)$alkyl, X represents halogen such as chlorine or bromine, which comprises hydrolysis and halogenation of an ester of formula (III)



(III)

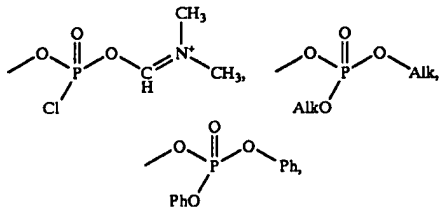
by photochemical irradiation in one pot using a halogenating agent in the absence or presence of a solvent at a temperature in the range of -20° C. to 30° C.

2. The process according to claim 1, wherein the solvent used is selected from diisopropyl ether, dichloromethane, acetic acid or mixtures thereof.

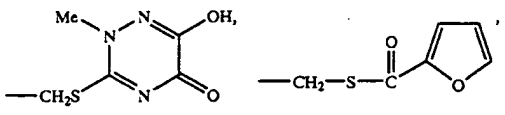
3. The process according to claim 1, wherein the halogenating agent used is chlorine or bromine.

4. The process according to claim 1, wherein the light source used for photochemical halogenation is IR or UV radiation.

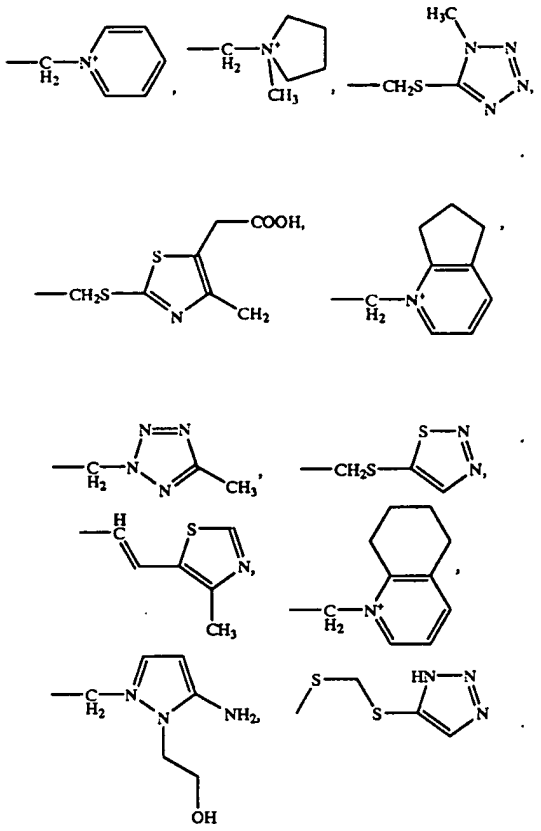
5. A process for the preparation of cephalosporin antibiotic of formula (II)



wherein R_1 represents CH_3, $CR^aR^bCOOR^c$ where R^a and R^b independently represent hydrogen or methyl and R^c represents hydrogen or $(C_1$-$C_3)$alkyl; R_2 represents H, CH_3, CH_2OCH_3, CH_2OCOCH_3, $CH{=}CH_2$,

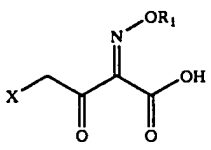


-continued



R_3 is carboxylate ion or $COOR^d$, where R^d represents hydrogen, esters which form a prodrug or a counter ion which forms a salt, by the condensation of an acid of formula (I) thus produced with 7-amino cephem derivative of formula (V) according to any of the preceding claims, said process comprising:

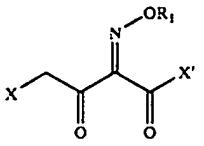
(i) activating 4-halogeno-2-substitutedimino-3-oxo-butyric acid of formula (I)



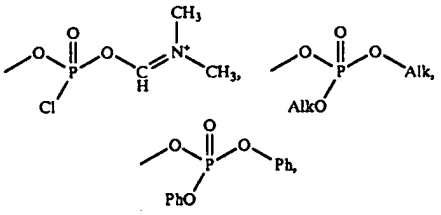
(I)

wherein R_1 represents CH_3, $CR^aR^bCOOR^c$ where R^a and R^b independently represent hydrogen or methyl and R^c represents hydrogen or $(C_1$-$C_3)$alkyl, X represents halogen such as chlorine or bromine, using conventional activation agents at a temperature in the range of -50° C. to 10° C. to produce a compound formula (IV)

(IV)



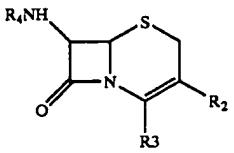
wherein X and R_1 are as defined earlier and X' represents halogen such as chlorine or bromine or other activating groups selected from



where Alk group represents (C_1-C_4)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or iso-butyl,

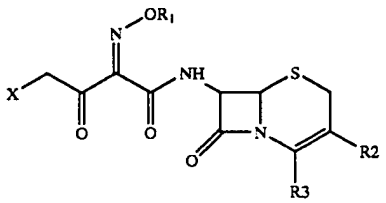
(ii) condensing the activated compound of formula (IV) with 7-amino cephem derivative of formula (V)

(V)



wherein R_4 is hydrogen or trimethylsilyl, R_2 and R_3 are as defined above, in the presence of a solvent at a temperature in the range of −50° C. to 10° C. to produce a compound of formula (VI)

(VI)



where all symbols are as defined above,

(iii) cyclising the compound of formula (VI) with thiourea in the presence of water miscible solvents at room temperature to produce cephalosporin compounds of formula (II) where all symbols are as defined earlier, and

(iv) optionally converting the compound of formula (II) to its pharmaceutically acceptable salts.

6. The process according to claim 5, wherein the activation in step (i) is carried out using PCl_5, DMF/$POCl_3$, oxalyl chloride, $SOCl_2$/DMF, diphenylchlorophosphoridate or dialkyl chlorophosphoridate.

7. The process according to claim 5, wherein the solvent used in step (i) is selected from halogenated alkanes, ethyl acetate, tetrahydrofuran, aromatic hydrocarbons, acetone, acetonitrile, dialkylethers or mixtures thereof.

8. The process according to claim 5, wherein the solvent used in step (ii) is selected from halogenated alkanes, ethyl acetate, tetrahydrofuran, aromatic hydrocarbons, acetone, acetonitrile, dialkylethers or mixtures thereof.

9. The process according to claim 5, wherein the cyclisation in step (iv) is carried out using a mixture of water and organic solvent selected from tetrahydrofuran, acetone, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane, (C_1-C_3)alcohol or mixtures thereof, in the presence of sodium acetate.

10. The process according to claim 5, wherein the counter ion represented by Rd is alkali metal.

11. The process according to claim 10, wherein the alkali metal is sodium.

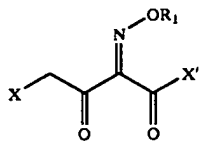
12. The process according to claim 5, wherein the prodrug ester represented by R^d is —(CH_2)—O—C(=O)—$C(CH_3)_3$, —$CH(CH_3)$—O—C(=O)—CH_3 or —$CH(CH_3)$—O—C(=O)—O—$CH(CH_3)_2$.

13. The process according to claim 5, wherein the compound of formula (I) obtained is a syn-isomer.

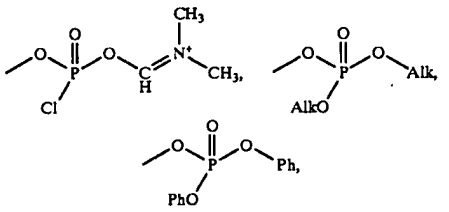
14. The process according to claim 5, wherein the condensed compound of formula (VI) can be cyclised with thiourea without isolation.

15. A novel intermediate of formula (IV)

(IV)



wherein X represents halogen such as chlorine or bromine, R_1 represents CH_3, $CR^aR^bCOOR^c$ where R^a and R^b independently represent hydrogen or methyl and R^c represents hydrogen or (C_1-C_6)alkyl and X' represents chlorine, bromine or an activating group selected from



where Alk group represents (C_1-C_4)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or iso-butyl.

* * * * *

US005109131A

United States Patent [19]

Naito et al.

[11] Patent Number: 5,109,131

[45] Date of Patent: Apr. 28, 1992

[54] METHOD FOR PRODUCTION OF T-BUTYL 3-OXOBUTYRATES AND THEIR USE

[75] Inventors: Kenzo Naito, Kyoto; Yukio Ishibashi, Osaka; Haruo Shinbo, Hyogo, all of Japan

[73] Assignee: Takeda Chemical Industries, Ltd., Osaka, Japan

[21] Appl. No.: 295,516

[22] Filed: Jan. 11, 1989

[30] Foreign Application Priority Data

Jan. 14, 1988 [JP] Japan 63-6133
Jun. 29, 1988 [JP] Japan 63-161984

[51] Int. Cl.[5] C07D 501/36

[52] U.S. Cl. 540/227; 540/222; 540/225

[58] Field of Search 540/228, 225, 226, 221, 540/222, 227

[56] References Cited

U.S. PATENT DOCUMENTS

4,399,132 8/1983 Curran et al. 424/246

FOREIGN PATENT DOCUMENTS

2012276 7/1979 United Kingdom .

OTHER PUBLICATIONS

Sven-Olov Lawesson et al., "Acetoacetic Acid, Tert-butyl Ester", Organic Syntheses, vol. 42, (1962) pp. 28-29.

Stephen R. Wilson et al., "The Ester Enolate Carroll Rearrangement", J. Org. Chem., vol. 49, (1984) pp. 722-725.

Primary Examiner—Nicholas S. Rizzo

Attorney, Agent, or Firm—Wegner, Cantor, Mueller & Player

[57] ABSTRACT

Disclosed are an advantageous method of industrial production of tert-butyl 3-oxobutylate, which is a useful intermediate for synthesis, characterized by reacting tert-butyl alcohol with diketene in the presence of 4-(tertiary amino) pyridine, and an industrially advantageous method of producing cephalosporin compounds or pharmaceutically acceptable salts thereof, using tert-butyl 3-oxobutylate as an intermediate.

9 Claims, No Drawings

METHOD FOR PRODUCTION OF T-BUTYL 3-OXOBUTYRATES AND THEIR USE

The present invention relates to an advantageous method of industrial production of tert-butyl 3-oxobutyrate useful as an intermediate for synthesis, especially as an intermediate for synthesizing cephalosporin compounds, and also relates to an industrially advantageous method of producing a cephalosporin compound using tert-butyl 3-oxobutyrate as an intermediate.

tert-Butyl 3-oxobutyrate is an important intermediate for synthesis in various industrial fields of, for example, agricultural chemicals, medicines, dyestuff or the like.

The use as intermediate for synthesis is described in, for example, "Chemical Reviews" 86, pp.248 to 249(1986), "Organic Synthesis Collective" 5, pp.155 to 157(1962), etc. And, tert-butyl 3-oxobutyrate is useful, in the pharmaceutical industry, as an important synthetic intermediate in the production of aminothiazole cephalosporins represented by, for example, cefmenoxime. Several kinds of aminothiazole cephalosporins have already been put on the market as antibiotics having a remarkably broad antimicrobial spectrum and have been widely used clinically. The chemical structures, pharmacological activities and production methods are described in "Angewandte Chemie: International Edition in English" 24, pp.180 to 202(1985), "Journal of Antibiotics" 38, pp. 1738 to 1751(1985), etc. In these methods of producing aminothiazole cephalosporins, it is tert-butyl 3-oxobutyrate that is used as the synthetic intermediate of the aminothiazole moiety. Methods of producing aminothiazole cephalosporins using tert-butyl 3-oxobutyrate as the synthetic intermediate are described in, for example, "Journal of Antibiotics" 38, p.p.1738 to 1751(1985), U.S. Pat. No. 4107380, U.S. Pat. No. 4191673, etc.

And, tert-butyl 3-oxobutyrate is conventionally prepared by a process which comprises allowing tert-butyl alcohol to react with diketene in the presence of sodium acetate ["Organic Synthesis" 42 p.p.28 to 29, 1962)], etc.

In conventional processes of producing tert-butyl 3-oxobutyrate, however, there are such drawbacks as set forth below:

(1) the reaction is necessarily conducted at relatively high temperatures(110° to 115° C.)(resulting in intense coloration of the reaction mixture, giving dehydroacetic acid as a by-product and, in most cases, necessitating a refining process of, e.g. distillation, before feeding the product to the subsequent reaction step), or

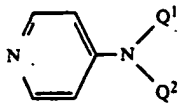
(2) the yield is not always high.

Therefore, the conventional methods cannot be considered as industrially advantageous ones.

The present inventors conducted various studies on industrially advantageous methods of producing tert-butyl 3-oxobutyrate, and as a result, found that tert-butyl 3-oxobutyrate can be obtained in a high purity and a high yield unexpectedly under such mild conditions as requiring no heating or cooling from outside by allowing tertiary butyl alcohol to react with diketene in the presence of 4-(tertiary amino)pyridine and that the thus-obtained reaction mixture of tert-butyl 3-oxobutyrate can be used as the material for the subsequent process without purification. On the basis of these findings, the present invention was accomplished.

Namely, the present invention relates to a method of producing tert-butyl 3-oxobutyrate, which is characterized by allowing tertiary butyl alcohol to react with diketene in the presence of 4-(tertiary amino)pyridine.

As the 4-(tertiary amino)pyridine, use is made of pyridines having tertiary amino groups substituted at the 4-position. As such pyridines, use is made of, among others, compounds represented by the formula:



(1)

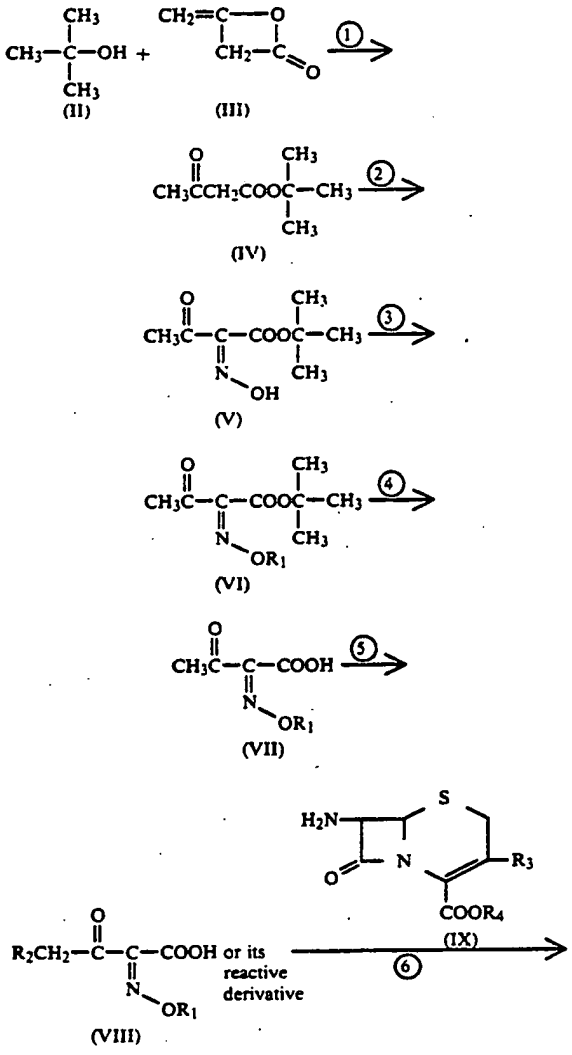
wherein Q^1 and Q^2 independently stand for an alkyl group or they are combined together with the adjacent nitrogen atom to form a cyclic amino group. In the formula(I), as the alkyl groups shown by Q^1 or Q^2, use is made of a lower alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, etc. And, as the cyclic amino group shown by Q^1 and Q^2 combinedly together with the adjacent nitrogen atom, use is made of, for example, a piperidino, 4-methyl piperidino or pyrrolidino group. Specific examples of the pyridines(I) include 4-(dimethylamino)pyridine, 4-(diethylamino)pyridine, 4-(di-n-propylamino)-pyridine, 4-(diisopropylamino)pyridine, 4-(N-methyl-N-ethylamino)-pyridine, 4-(N-ethyl-N-n-propylamino)-pyridine, 4-pyrrolidinopyridine, 4-(4-methylpyrrolidino)pyridine, 4-piperidinopyridine, etc. These 4-(tertiary amino)pyridines can be recovered after finishing this reaction and can be used repeatedly. Examples of preferable 4-(tertiary amino)pyridine include 4-(di-C_{1-3} alkylamino)pyridine such as 4-(dimethylamino)-pyridine. 4-(tertiary amino)pyridine can accelerate the reaction in a catalytic amount, i.e., usually 0.001 to 1 mol. relative to 1 mol. of tert-butyl alcohol, preferably 0.001 to 0.02 mol.

This reaction is conducted usually in the absence of solvent, but it may be carried out in a non-protonic organic solvent which does not give undesirable effects upon the reaction. Examples of such non-protonic organic solvents include nitriles such as acetonitrile, ethers such as tetrahydrofuran, 1,2-dimethoxyethane, dioxane or diethylether, halogenated hydrocarbons such as methylene chloride, chloroform or carbon tetrachloride, esters such as ethyl acetate, butyl acetate, amides such as N, N-dimethylformamide or N,N-dimethylacetamide, hydrocarbons such as benzene, toluene, xylene, hexane or pentane, or a mixture of them. The volume of such non-protonic organic solvent to be used is in the range of from 0.2 to 20 l relative to 1 mol. of tert-butyl alcohol, preferably 1 to 5 l. The amount of diketene to be used is usually 1 mol. relative to 1 mol. of tertiary butyl alcohol, but it may be in the range of from 0.5 to 1.5 mol. This reaction can also be carried out by adding diketene dropwise to a mixture of tert-butyl alcohol and 4-(tertiary amino)pyridine, and, in this case, unexpectedly, the object of this reaction can be attained even in the absence of solvent. The reaction temperature usually ranges from 0° C. to 100° C., preferably from 25° C. to 80° C. Since the present reaction is exothermic, no heating is required at all for maintaining the above-mentioned temperature range. When the reaction temperature rises too high by the heat of the reaction, the reaction temperature can easily be adjusted within the range by using industrial cooling water or the like. And, it is not necessary at all to adjust the reaction temperature to 0° C. or lower by using a cooling agent

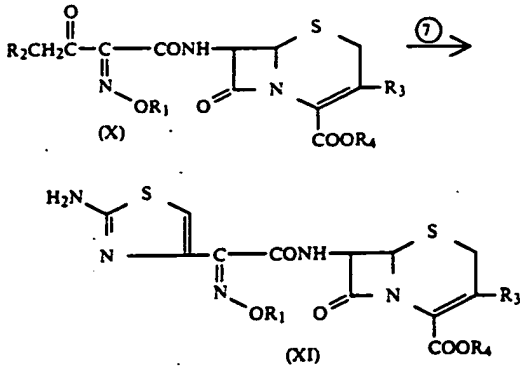
such as liquid nitrogen, etc., which has so far been considered to be indispensable to prevent the polymerization of diketene per se. For maintaining such reaction temperature, it is preferable to add diketene dropwise. The time required for this dropwise addition usually ranges from 0.2 to 10 hours, preferably 0.3 to 3 hours, while the range is not specifically limited so long as the object can be attained. By adjusting the rate of dropwise addition of diketene, the reaction can be allowed to proceed without heating or cooling. The reaction time after completing the dropwise addition of diketene varies with the solvent then used, reaction temperature, etc., but it usually ranges from 0.2 to 5 hours, preferably from 0.3 to 2 hours.

The thus-obtained tert-butyl 3-oxobutyrate can be used as the material of the subsequent process in the state of the reaction mixture. Or, the reaction mixture can be used as the material of the subsequent process after isolation and purification by means of, for example, concentration, distillation, pH-change, solvent-extraction, chromatography, etc.

The thus-produced tert-butyl 3-oxobutyrate can be used for the production of cephalosporin compounds by the following reaction processes.



-continued



The process ① as explained above.

The process ② is carried out by allowing tert-butyl 3-oxobutyrate to react with a nitrosating agent. The agent is exemplified by nitrous acid, esters of nitrous acid such as methyl nitrite, ethyl nitrite, amyl nitrite, etc., nitrosyl halides such as nitrosyl chloride, etc. And, nitrous acid may be produced in the reaction system by allowing an alkali nitrite (e.g. sodium nitrite, etc.) to react with an acid (e.g. hydrochloric acid, acetic acid, etc.) This reaction is conducted usually in a solvent, and any solvent can be used unless it hampers the reaction. Practical examples of such solvent are dioxane, tetrahydrofuran, water, acetic acid or a mixture of these solvents.

The reaction can be carried out usually in the range of from −20° C. to 50° C. The reaction may go to completion in 5 minutes to 24 hours, preferably in a short time (20 minutes to 10 hours). The reaction product (V) can be subjected to the subsequent reaction after isolation by a conventional means or without isolation.

The process ③ can be carried out by allowing the thus-produced compound (V) to react with an alkylating agent. Specific examples of the alkylating agent include dialkyl sulfates such as dimethyl sulfate, diethyl sulfate, etc., diazoalkanes such as diazomethane, diazoethane, etc., alkyl halides such as methyl iodide, ethyl iodide, etc. and alkyl esters of sulfonic acid such as a methyl ester of p-toluenesulfonic acid.

The reaction employing dialkyl sulfate, alkyl halide or alkyl ester of sulfonic acid is carried out usually in water, acetone, ethanol, ether, dimetylformamide or any other solvent which does not give any undesirable influence upon the reaction. This reaction is carried out preferably in the presence of an inorganic or organic base. The reaction temperature is not specifically limited, but the reaction is carried out, in most cases, in the range of from cooling to heating up to about the boiling point of the solvent then used. The reaction time is usually 0.1 to 40 hours, preferably 0.5 to 12 hours.

The reaction employing diazoalkane is carried out usually in a solvent such as ether, tetrahydrofuran, etc. The reaction temperature is not specifically restrictive, but, usually within the range of from cooling to room temperatures.

The starting compound (V) may be an alkali metal salt such as sodium, potassium, etc. at the hydroxyimino group. The alkyl group which may be substituted as represented by R_1 in the compounds (VI) to (VIII), (X) and (XI) produced according to this invention may be, for example, C_{1-4} alkyl such as methyl, etc., or C_{1-4} alkyl optionally substituted with carboxyl, a C_{1-4} alkoxy-car-

bonyl or the like, for example, carboxymethyl, carboxypropyl, 1-carboxy-1-methylethyl, 1-tert-butoxycarbonyl-1-methylethyl, etc.

The process (4) is carried out by subjecting the thus-produced compound (VI) to de-esterification. The de-esterification is conveniently carried out by allowing the compound (VI) to react with hydrogen halide. As the hydrogen halide, use is made of, for example, hydrogen chloride, hydrogen bromide, etc. and, preferably hydrogen chloride.

This reaction is carried out preferably in an anhydrous organic solvent. As the organic solvent, any one which does not adversely affect the reaction can be used, for example, nitriles such as acetonitrile etc., ethers such as tetrahydrofuran, 1,2-dimethoxyethane, dioxane, diethyl ether, etc., halogenated hydrocarbons such as carbon tetrachloride, etc., esters such as ethyl acetate, butyl acetate, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., hydrocarbons such as benzene, toluene, xylene, hexane, pentane, etc., or a mixture of these solvents, and, above all, halogenated hydrocarbons(especially chlorinated hydrocarbon such as methylene chloride) are often used as preferable ones. The volume of such organic solvent is usually 0.1 to 10 l relative to 1 mol. of the compound (VI), preferably 0.5 to 2 l. Presence of water in the reaction mixture accelerates occurrence of by-products, and, therefore, it is preferable to minimize the amount of water in the reaction mixture as far as possible. For that purpose, as the above-mentioned organic solvents, such containing as little water as possible, i.e. it is desirable to employ substantially anhydrous ones.

This reaction can be carried out conveniently by allowing the compound (VI) to react with hydrogen halide in an anhydrous organic solvent. More specifically, this reaction is usually carried out being catalyzed by hydrogen halide gas, which is blown into the compound (VI) in an anhydrous organic solvent, when desired under elevated pressure or while stirring. The reaction may also be effected by dissolving the hydrogen halide in advance in the anhydrous organic solvent employed, if desired under pressure or with stirring, and then adding the tert-butyl 2-substituted oxyimino-3-oxobutyrate to the thus-prepared solution. The hydrogen halide is used generally in an amount of 1 to 10 moles, preferably 1 to 6 moles, per mole of tert-butyl 2-substituted oxyimino-3-oxobutyrate, although said amount may vary depending on the organic solvent employed. When, in particular, an alkylene chloride, such as methylene chloride, which is preferred as the organic solvent, is used, the hydrogen halide is used generally in an amount of 1 to 3 moles, preferably 1.2 to 2 moles, per mole of tert-butyl 2-substituted oxyimino-3-oxobutyrate.

The reaction temperature is not critical. The only requirement is that the reaction can proceed at the temperature employed. Generally, however, the reaction is carried out at −50° C. to 80° C., preferably 0° C. to 30° C. The hydrogen halide is blown into the starting material-solvent mixture generally over a period of 0.5 to 20 hours, preferably 2 to 10 hours, although the period of hydrogen halide feeding should be varied depending on the reaction temperature, the solvent and the hydrogen halide quantity. Then, the reaction mixture is recommendably stirred or allowed to stand generally for 1 to 24 hours, preferably 2 to 15 hours. In case where the hydrogen halide is dissolved in advance in the solvent, for example, by blowing into the reaction system, it is preferable to stir usually for 1 to 40 hours, preferably 2 to 20 hours after the addition of the compound (VI), while varying with the reaction temperatures, solvents used, the amount of hydrogen halide used, etc.

The compound (VII) produced by the reaction can be subjected to the subsequent reaction as in the state of the reaction mixture or after isolation and purification by conventional means such as concentration, pH change, solvent extraction, crystallization, recrystallization, chromatography, etc.

The process (5) comprises subjecting the thus-produced compound (VII) to halogenation to obtain the compound (VIII).

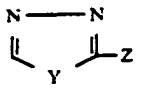
As the halogenating agent for this halogenation, use is made of, for example, halogen (chlorine, bromine, iodine, etc.), halogenated sulfuryl (sulfuryl chloride, etc.), N-halogenosuccinimide (N-bromosuccinimide, N-chlorosuccinimide, etc.), 1,3-dibromo-5,5-dimethylhydantoin, etc., and, especially, bromine, sulfuryl chloride, N-bromosuccinimide, etc. are often used. These halogenating agents are used usually in an amount of 0.5 to 1.5 mol. relative to the compound (VII). This halogenation is carried out usually in a solvent. As the solvent, any one which does not affect the reaction adversely can be employed, as exemplified by hydrocarbons such as hexane, benzene, toluene, xylene, etc., ethers such as tetrahydrofuran, isopropyl ether, dioxane, diethyl ether, etc., halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride, etc., esters such as ethyl acetate, etc., ketones such as acetone, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc. or a mixture thereof. Preferable solvents are exemplified by halogenated hydrocarbons such as methylene chloride, etc., ethers such as tetrahydrofuran, etc., etc. The reaction temperatures are not specifically limited so long as the desired halogenation proceeds, and, usually ranging from −50° C. to 80° C., preferably from −20° C. to 30° C. Anhydrous acid catalysts can also be employed, which are exemplified by inorganic acids such as hydrogen chloride, hydrogen bromide, sulfuric acid, phosphoric acid, dichlorophosphoric acid, etc., organic acids such as formic acid, acetic acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, etc., Lewis acids such as boron fluoride, aluminium chloride, titanium tetrachloride, etc., etc. A preferable anhydrous acid catalyst is exemplified by commercially available acetic acid solution of hydrogen bromide. And, in this halogenation, as the starting material, the compound (VII) produced by the process (4) can be employed as in the state of the reaction mixture. In this case, an excess portion of the hydrogen halide used in the process (4) can be employed as the anhydrous acid catalyst in this halogenation reaction. Therefore, it is advantageous from the viewpoint of industrial large scale production to carry out this halogenation succeeding the process (4). The reaction time varies with the solvents, halogenating agents, anhydrous acid catalysts, reaction temperatures and any other conditions then employed, and it is usually in the range of from 0.5 to 20 hours, preferably 1 to 6 hours.

Thus-obtained compound (VIII) may be used as the synthetic intermediate as in the state of the reaction mixture, or after isolation and purification by conventional means such as concentration, pH change, solvent extraction, crystallization, recrystallization, chromatography, etc. Typical examples of thus-obtained com-

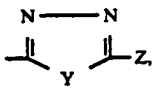
pound (VIII) are set forth as follows: (i) 4-chloro-2-methoxyimino-3-oxobutyric acid (ii) 4-bromo-2-methoxyimino-3-oxobutyric acid (iii) 4-iodo-2-methoxyimino-3-oxobutyric acid

The process (6) comprises allowing the compound (VIII) or a reactive derivative thereof to react with the compound (IX) or a salt thereof to produce the compound (X) or a salt thereof. R_2 in the formulae (VIII) and (X) stands for a halogen atom such as chlorine, bromine, fluorine, iodine, etc., and usually chlorine and bromine are employed.

The substituent R_3 on the cephem ring in the formulae (IX) and (X) stands for hydrogen atom, $-CH_2R_5$ (R_5 stands for hydrogen atom or the residual group of a nucleophilic compound), halogen atom, an optionally substituted hyroxyl group, lower alkenyl group having 2 to 4 carbon atoms (e.g. vinyl group, 1-propenyl group, etc.), thiol group or amino group or



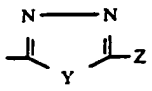
wherein Y stands for oxygen atom, sulfur atom or an optionally substituted imino group, Z stands for hydrogen atom or an optionally substituted hydroxyl group, amino group, thiol group or hydrocarbon group. R_5 stands for hydrogen or the residual group of a nucleophilic compound, and examples of the residual group R_5 include a hydroxyl group, mercapto group, a lower aliphatic acyloxy group having 2 to 4 carbon atoms which may optionally be substituted by oxo, carboxyl, C_{1-4} alkoxycarbamoyl or the like, such as acetyloxy group, propionyloxy group, 3-oxobutyryloxy group, 3-carboxypropionyloxy group, 3-ethoxycarbamoylpropionyloxy group, 4-carboxybutyryloxy group, etc., an aromatic acyloxy group which may optionally be substituted by hydroxyl, carboxy, C_{1-4} alkoxy-carbonylcarbamoyl, C_{1-4} alkoxy-carbonylsulfamoyl or the like, such as mandelyloxy group, 2-carboxybenzoyloxy group, 2-(carboethoxycarbamoyl)benzoyloxy group, 2-(carboethoxysulfamoyl)benzoyloxy group, etc., carbamoyloxy group, cyano, azido, amino, carbamoylthio, thiocarbamoyloxy, carbamoyloxy group wherein the amino group is protected with the conventional protective group for amino (e.g. N-mono-, di- and trihalogenoacetylcarbamoyloxy group such as N-chloroacetylcarbamoyloxy group, N-dichloroacetylcarbamoyloxy group, N-trichloroacetylcarbamoyloxy group, etc., N-chlorosulfonylcarbamoyloxy group, N-trimethylsilylcarbamoyloxy group), and phenylglycyloxy group, or these residual groups of nucleophilic compounds may be further substituted with an alkyl group(e.g. C_{1-3} lower alkyl group such as methyl, ethyl, propyl, etc.) or an acyl group (e.g. C_{2-4} lower aliphatic acyl group such as acetyl, propionyl, butyryl, etc., or an aromatic acyl such as benzoyl, p-chlorobenzoyl, p-methylbenzoyl, mandeloyl, etc.), and, in this case, the number of substituents is usually 1 to 2. Or, the residual group R_5 may be a quaternary ammonium group, and it also stands for a heterocyclic group bonded through S, namely heterocyclic thio group. The heterocyclic thio group has a 5- or 6-membered ring containing 1 to 4 hetero-atoms selected from O, S or N, and the nitrogen atom may be in the form of oxide. As these heterocyclic groups, use is often made of, for example, pyridyl, N-oxidopyridyl, pyrimidyl, pyridazinyl, N-oxidopyridazinyl, pyrazolyl, imidazolyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, oxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H-tetrazolyl, 2-tetrazolyl, etc. And, these heterocyclic thio groups may have on the heterocyclic ring substituent(s) including a C_{1-3} lower alkyl group such as methyl, ethyl, propyl, etc., a C_{1-3} lower alkoxy group such as methoxy, ethoxy, propoxy, etc., a halogen atom such as chlorine, bromine, etc., trihalogeno-substituted C_{1-3} alkyl such as trifluoromethyl, trichloroethyl, etc., hydroxyl group, mercapto group, amino group, carboxyl group, carbamoyl group, a di-C_{1-3} alkylamino-C_{1-3} alkyl group such as dimethylaminoethyl, dimethylaminomethyl, etc., carboxymethyl group, etc. The number of these substituents is usually 1 to 2. As the quaternary ammonium group shown by R_5, use is often made of, for example, pyridinium, 3-methylpyridinium, 4-methylpyridinium, 3-chloropyridinium, 3-bromopyridinium, 3-iodopyridinium, 4-carbamoylpyridinium, 4-(N-hydroxymethylcarbamoyl)-pyridinium, 4-(N-carbomethoxycarbamoyl)pyridinium, 4-(N-cyanocarbamoyl)pyridinium, 4-(carboxylmethyl)-pyridinium, 4-(hydroxymethyl)pyridinium, 4-(trifluoromethyl)-pyridinium, quinolinium, picolinium or lutidinium, etc. And, when R_3 stands for halogen atom, optionally substituted hydroxyl group, C_{2-4} alkenyl group, thiol group or amino group, as the halogen atom, use is made of, for example, chlorine, bromine, etc. as mentioned above. The hydroxyl group, C_{2-4} alkenyl group, thiol group or amino group may be respectively substituted. As the substituents, use is made of, for example, a hydrocarbon group e.g. alkyl (preferably C_{1-4}) such as methyl, ethyl, etc., aralkyl (preferably C_{7-9}) such as benzyl, etc., and C_{6-10} aryl such as phenyl, etc., acyl group (preferably C_{2-8}) such as acetyl, benzoyl, etc. and so on, and these substituents may be further substituted with carboxyl group, sulfo group, hydroxyl group, etc. And, in the case of amino group, are included pyrrolidino, morpholino, thiomorpholino, etc. formed by linkage with the N-atom. Specific examples include hydroxyl group, methoxy group, ethoxy group, methylthio group, carboxymethylthio group, phenylthio group, amino group, dimethylamino group, ethylamino group, 2-dimethylaminoethyl group, chlorine, bromine, etc. And, when R_3 stands for



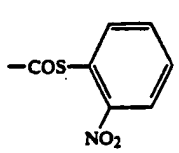
Y stands for oxygen atom, sulfur atom or an optionally substituted imino group. Examples of substituents of the optionally substituted imino group include a lower alkyl group (preferably having 1 to 3 carbon atoms) such as methyl, ethyl, etc., or a lower alkyl group (preferably having 1 to 4 carbon atoms) substituted with hydroxyl group, mercapto group, amino group, morpholino group, carboxyl group, sulfo group, carbamoyl group, alkoxycarbonyl group (preferably having 2 to 6 carbon atoms), lower alkylcarbamoyl group (preferably having 2 to 6 carbon atoms), alkoxy group (preferably 1 to 4 carbon atoms), alkylthio group (preferably 1 to 4 carbon atoms), alkylsulfonyl group (preferably 1 to 4 carbon atoms), acyloxy group (preferably 2 to 4 carbon atoms) or morpholinocarbonyl group, C_{6-10} aryl group

such as phenyl group, etc., C_{7-10} aralkyl group such as benzyl group, etc., acyl group (preferably having 1 to 5 carbon atoms) such as acetyl group, propionyl group, benzoyl group, etc. Examples of the substituents of hydroxyl group, amino group, thiol group or hydrocarbon group [for example, alkyl groups (preferably having 1 to 4 carbon atoms) such as methyl, ethyl, propyl, isobutyl, tert-butyl, etc., C_{7-10} aralkyl group such as benzyl, etc., C_{6-10} aryl group such as phenyl, naphthyl, etc., etc.] shown by Z include lower alkyl, acyl group, aralkyl group, aryl group, etc. as described in the foregoing. These substituents may be further substituted with carboxyl group, sulfo group, hydroxyl group, etc. And, in the case of amino group, there may be included cases where pyrrolidino group, morpholino group, thiomorpholino group, etc. may be formed together with the N-atom.

Specific examples of



include 5-acetylamino-1,3,4-thiadiazol-2-yl, 5-amino1,3,4-thiadiazol-2-yl, 5-dimethylamino-1,3,4-thiadiazol2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol2-yl, 5-acetamido-1,3,4-triazol-2-yl, 5-acetamido-1,3,4-oxadiazol-2-yl, etc. The optionally esterified carboxyl group shown by $-COOR_4$ in the formulae (IX), (X), and (XI) means carboxyl group or its inorganic or organic salts with alkali, alkaline earth metal or the like such as salts with sodium, potassium, triethylamine, etc., and further means esterified carboxyl group. Examples of these esters include methyl, ethyl, tert-butyl, tert-amyl, benzyl, p-nitrobenzyl, alkanoyloxymethyl (acetoxymethyl, etc.), di- or tri-alkylsilyl(trimethylsilyl, etc.), alkoxysilyl, benzhydryl, 1-indanyl, phthalidyl, 5-indanyl, phenacyl, phenyl, p-nitrophenyl, alkoxyalkyl (methoxymethyl, ethoxymethyl, etc.), alkenyl, trichloroethyl, methylsulfonylethyl, benzyloxymethyl, tert-butyl, methoxybenzyl, trityl, methylthiomethyl, pivaloyloxymethyl, α-acyloxy-α-substituted methyl such as α-acetoxybutyl, α-ethoxycarbonyloxy-α-methylmethyl, etc.-ester. These esters are desirably those which can be led to free form under such mild conditions as causing no opening of β-lactam ring. For example, use is made of such esters wherein R_4 can be converted to hydrogen under mild acid or alkaline conditions, e.g. diphenylmethyl, substituted phenyl, lower alkylsulfonylethyl, pivaloyloxymethyl, etc., or groups which can be eliminated by means of oxidation or reduction reaction, such as trichloroethyl group, benzyl group, etc. And, $-COOR_4$ includes such groups as



which can be readily hydrolyzed to convert into —COOH.

The compound (VIII) is subjected to acylation in the free state, or as a salt formed at the carboxyl group with an alkali or alkaline earth metal such as sodium, potassium or calcium, etc. or with an organic amine such as trimethylamine, pyridine, etc., or as a reactive derivative such as an acid halide (e.g. acid chloride, acid bromide), an acid anhydride, a mixed acid anhydride, an active amide, an active ester, etc. As the active ester, use is made of, for example, p-nitrophenylester, 2,4-dinitrophenylester, pentachlorophenylester, N-hydroxysuccinoimidoester or N-hydroxyphthalimidoester, etc. As the mixed acid anhydride, use is made of, for example, a mixed acid anhydride with a carbonic acid monoester such as monomethyl carbonate, monoisobutyl carbonate, or a mixed acid anhydride with a lower alkanoic acid optionally substituted with a halogen such as pyvalic acid or trichloroacetic acid, etc. When the compound (VIII) is used in the state of free acid or a salt, a suitable condensing agent is used. Examples of the condensing agent include N,N,-di-substituted carbodimides such as N,N-dicyclohexylcarbodimide, azolide compounds such as N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole, a dehydrating agent such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, alkoxyacetylene, etc., 2-halogeno-pyridinium salts (e.g. 2-chloropyridiniummethyliodide, 2-fluoropyridiniummethyliodide), etc. When such a condensing agent as above is used, it is considered that the reaction proceeds via a reactive derivative of the compound (VIII). The reaction is usually conducted in a suitable solvent. As the solvent, use is often made of halogenated hydrocarbon such as chloroform, methylene chloride, etc., ethers such as tetrahydrofuran, dioxane, etc., dimethylformamide, dimethylacetamide, acetone, water, etc. or a mixture of them. The amount of the compound (VIII) or its reactive derivative is usually about 1 to several mol. relative to 1 mol. of the compound (IX). The reaction temperature is generally in the range of from −50° C. to 40° C. The reaction time ranges usually from 10 minutes to 48 hours, preferably 30 minutes to 10 hours. The thus-obtained compound (X) can be isolated by a conventional means, but it is used as the starting material for the subsequent process. Leading of the compound (VIII) to its salt or a reactive derivative can be conducted by a per se known means to persons having ordinary skill in the art.

The process (7) comprises allowing the compound (X) thus produced or a salt thereof to react with thiourea to obtain the compound (XI) or a salt thereof. This reaction is carried out usually in a solvent. As the solvent, use is made of any one which does not hamper the reaction, as exemplified by water, methanol, ethanol, acetone, tetrahydrofuran, dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpiperidone, etc. or a mixture of them. The reaction is carried out under ice-cooling, at room temperature or under heating (−30° C. to 80° C.). The amount of the compound (XI) usually ranges from one to several equivalents relative to the compound (X), and the reaction time ranges from 1 to 48 hours, preferably 1 to 10 hours. The thus-obtained compound (XI) can be isolated and purified by conventional means such as concentration, concentration under reduced pressure, crystallization, recrystallization, solvent extraction, pH change, salting out, fractional distillation, distillation, chromatography, etc. The compounds shown by (V), (VI), (VII), (VIII), (X) and (XI) may be either syn-isomers or anti-isomers or a mixture of them. Both syn-isomers and anti-isomers are useful, but, in the compound (XI), syn-isomers are stronger than anti-isomers in antimicrobial activity, and,

therefore, in the compounds of (V), (VI), (VII), (VIII), (X) and (XI), syn-isomers are preferable.

As compared with conventional methods of producing tert-butyl 3-oxobutyrate, the method of this invention is excellent in, among others, the following respects:

(1) the reaction proceeds under mild conditions,
(2) the reaction can be allowed to proceed advantageously without using solvent,
(3) the reaction mixture is not colored,
(4) therefore, no decolorizing refining process is required for obtaining a colorless product, and the reaction mixture itself can be used as the starting material for the subsequent process, and
(5) the object product can be obtained in a high purity and in a high yield.

Thus, the method of this invention is remarkably advantageous for industrial production of tert-butyl 3-oxobutyrate. Consequently, in the industrial production of the final object product using tert-butyl 3-oxobutyrate as the synthetic intermediate, the method of this invention can be an advantageous one for producing the said synthetic intermediate. For example, according to the method of this invention, as described in detail in the foregoing, an aminothiazole type cephalosporin compound (XI) and salts thereof having excellent antimicrobial activity can be produced with an industrial advantage.

The following Working Examples are given below to illustrate the present invention in more detail, but these are not intended to limit the present invention in any way.

Symbols used in the Working Examples have the following significances. .

s: singlet, $CDCl_3$: deuteriochloroform, %: weight NMR (nuclear magnetic resonance spectrum): unless otherwise specified, measured by using tetramethylsilane as the internal standard at 90 MHz, and showing the values of chemical shift with δ(ppm).

WORKING EXAMPLE 1

To a mixture of tert-butyl alcohol [74.1 g] and 4-(dimethylamino)pyridine [0.61 g] was added dropwise diketene [84.1 g] at 50° to 60° C. in the course of one hour while stirring. The stirring was continued for one further hour at 30° to 50° C. to obtain a colorless and clear reaction mixture, which was subjected to distillation under reduced pressure (b.p. 85° C./20 mmHg) to yield tert-butyl 3-oxobutyrate [156 g] as an oily product. The yield was 98.6%. NMR($CDCl_3$): δ3.34(2H,s), 2.25(3H,s), 1.47(9H,s)ppm .

WORKING EXAMPLE 2

(Method of preparing tert-butyl 2-methoxyimino-3-oxobutyrate)

To a mixture of tert-butyl alcohol [741.2 g] and 4-(dimethylamino)pyridine [6.1 g] was added dropwise diketene [840.7 g] at 50° to 60° C. in the course of one hour while stirring. The stirring was continued for one further hour at 30° to 50° C. To the colorless and clear reaction mixture thus obtained was added acetic acid [1501 g]. To the resultant solution was added dropwise a solution of sodium nitrite [773.2 g] in water [1.35 l] at 5° to 9° C. in the course of 1.5 hour, followed by stirring for 1.5 hour at 8° to 18° C. To the reaction mixture were added toluene [1.42 l] and a 5% aqueous solution of sodium chloride [1.3 l], to which was then added sodium hydroxide [600 g] in water [1.1 l] to render the pH to 6.7. The reaction mixture was separated into two layers, and the aqueous layer was subjected to extraction with toluene (0.7 l). The extract was combined with the toluene layer and washed with a 5% aqueous solution of sodium chloride (1.2 l), from which toluene was distilled off under reduced pressure to leave crude product of tert-butyl 2-hydroxyimino-3-oxobutyrate as a viscous oily substance.

To the tert-butyl 2-hydroxyimino-3-oxobutyrate was added water [6 l], to which was added 30% sodium hydroxide [800 ml] at 28° C. while stirring to render the pH to 9.0. To the resultant solution was added dimethyl sulfate [1324 g] at 28° to 30° C. in the course of 20 minutes, which was stirred for 4 hours while adding thereto at 25° to 30° C. a 30% aqueous solution of sodium hydroxide [500 ml] to adjust the pH within the range of 8.7 to 9.0. After completion of the reaction, extraction was conducted with methylene chloride [4 l], and the aqueous layer was subjected to further extraction with methylene chloride [2 l]. The methylene chloride layers were combined and washed with a 1N aqueous solution of sodium hydroxide, 1N HCl, a 5% aqueous solution of sodium hydrogencarbonate and water, each one litre portion, successively. The resultant solution was dried over anhydrous sodium sulfate [700 g], followed by concentration under reduced pressure to obtain tert-butyl 2-methoxyimino-3-oxobutyrate [1878 g] as an oily product. The yield was 93.3%. NMR($CDCl_3$): δ4.08 (3H,s), 2.36(3H,s), 1.53(9H,s)ppm .

WORKING EXAMPLE 3

(1) In methylene chloride [2.8 l] was dissolved tert-butyl 2-methoxyimino-3-oxobutyrate [805 g] obtained in Working Example 2. Into this solution was introduced hydrogen chloride [210 g] by blowing at 3° to 6° C. in the course of 8 hours, followed by leaving the system standing for 15 hours at 5° C. The supernatant was concentrated to dryness to obtain 2-methoxyimino-3-oxobutyrate [556 g] as a crystalline solid matter. The yield was 95.8%. NMR($CDCl_3$): δ4.17(3H,s), 2.44(3H,s) ppm. (2) In methylene chloride [3 l] was dissolved 2-methoxyimino-3-oxobutyric acid [460 g] obtained in the above operation (1). To the solution was added a 25% solution of hydrogen bromide in acetic acid [46 ml]. To this solution was added dropwise at 7° to 15° C. a solution of bromine [372 g] in methylene chloride [372 ml] in the course of 2 hours. Then, nitrogen was vigorously blown into the system for 30 minutes at 7° to 8° C. to eliminate hydrogen bromide which formed as the by-product. To the supernatant were added silica gel (Kieselguhr 60, 70 to 230 mesh, manufactured by Merck) [80 g] and activated charcoal (Shiragi coarse particles, manufactured by Takeda Chemical Industries, Ltd.) [30 g]. The mixture was stirred at 10° to 15° C. for 30 minutes, followed by filtration to remove insolubles. The filtrate was concentrated under reduced pressure, and the residual oily substance was dissolved in xylene [685 ml], which was left standing at 5° C. for 15 hours. Precipitating crystals were collected by filtration, and the crystals were washed with a mixture of xylene and n-hexane [1:1(V/V)] [100 ml] and n-hexane [200 ml], followed by drying under reduced pressure to obtain 4-bromo-2-methoxyimino-3-oxobutyric acid [434 g]. The filtrate was concentrated under reduced pressure. To the residual oily substance was added a mixture of xylene and n-hexane [100:15 (V/V)] [238 ml] to cause crystalliza-

tion to obtain further 4-bromo-2-methoxyimino-3-oxobutyric acid [82.3 g]. The yield was 72.7%.

NMR($CDCl_3$): δ4.36(2H,s), 4.20(3H,s), ppm

(3) To methylene chloride [50 ml] was added phosphorus pentachloride [2.62 g], and the mixture was stirred, to which was added, while cooling at 0° to 5° C., 4-bromo-2-methoxyimino-3-oxo-butyric acid [2.06 g] obtained in the above (2). The mixture was stirred at the same temperature range for one hour. To the reaction mixture was added water [25 ml], which was stirred, followed by separating into two layers. The organic layer was washed with water [5 ml] and subjected to distillation under reduced pressure to remove the solvent. The residue was dissolved in tetrahydrofuran [5 ml] to give a solution of 4-bromo-2-methoxyimino-3-oxobutyryl chloride.

(4) In a mixture solvent of water [12 ml] and tetrahydrofuran [7 ml] were dissolved 7β-amino-3-(1,2,3-thiadiazole-5-yl)thiomethyl-3-cephem-4-carboxylic acid [1.65 g] and sodium hydrogencarbonate [1.68 g]. To the solution was added the solution of 4-bromo-2-methoxyimino-3-oxobutyryl chloride obtained in the above (3). The mixture was stirred at 20° to 25° C. for 5 minutes to allow 7β-[4-bromo-2-methoxyimino-3-oxobutylamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid to be produced in the reaction mixture. To the reaction mixture was then added a solution of thiourea [1.52 g] dissolved in a mixture of water [3 ml] and tetrahydrofuran [3 ml], and the whole mixture was stirred for one hour at the same temperature range. To the resultant mixture was added sodium chloride [3.7 g], which was stirred for three hours at 5° to 10° C. Precipitating solid matter was collected by filtration and washed with tetrahydrofuran [15 ml], followed by drying under reduced pressure to afford sodium salt of 7β-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid [2.35 g]. The yield was 87.9%.

COMPARATIVE EXAMPLE

[Method described in Organic Synthesis, 42, pp.28 to 29 (1962)]

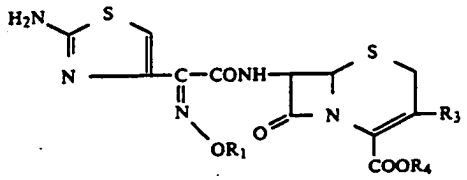
To tert-butyl alcohol [79 g (1.07 mol.)] heated at 80° to 85° C. was added, while stirring, anhydrous sodium acetate [0.4 g (4.8 mmol.)]. To the mixture was then added dropwise diketene [96 g (1.14 mol.)] in the course of 2.5 hours. During the initial 15 minutes, the addition was carried out at 60° to 70° C., then while heating up to 110° to 115° C. After the dropwise addition of diketene, the resulting blackish brown reaction mixture was stirred for further 30 minutes, immediately followed by distillation under reduced pressure to afford tert-butyl 3-oxobutyrate, b.p. 85° C./20mmHg. The yield was 135 g (80%).

(1) The reaction mixture obtained by the known method in this Comparative Example is, as apparent from the above, colored blackish brown. Therefore, in order to obtain a colorless product from the above-mentioned reaction mixture, a decolorizing purification process is inevitably necessary. On the other hand, the reaction mixture of tert-butyl 3-oxo-butyrate obtained by the method of this invention is colorless and clear, as apparent from the above Working Examples 1 and 2, and no decolorizing purification process is required. Accordingly, it is apparent that the method of this invention for preparing tert-butyl 3-oxobutyrate is remarkably superior to conventional methods from an industrial viewpoint, because the process of decolorizing purification of the reaction mixture can be saved.

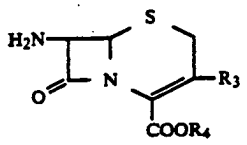
(2) The yield (weight %) of the product obtained by the method of the present invention was, as apparent from Working Example 1, 98.6%, while that of the product obtained by the conventional method in the above Comparative Example was 80%, i.e. the former being higher than the latter by about 19%. Therefore, the method of the present invention is superior to conventional ones in respect of the yield as well.

What we claim is:

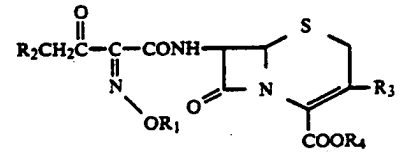
1. A method of producing a cephalosporin compound of the formula:



wherein R_1 stands for a C_{1-4} alkyl group optionally substituted with carboxyl or a C_{1-4} alkoxy-carbonyl group, R_3 stands for hydrogen atom or a standard cephalosporin substituent and R_4 stands for hydrogen atom or a group which can be converted to hydrogen under mild acid or alkaline conditions or eliminated by means of oxidation or reduction, or a salt thereof, which is characterized by allowing tert-butyl alcohol to react with diketene in the presence of 4-(tertiary amino)pyridine to give tert-butyl 3-oxobutyrate, by allowing the tert-butyl 3-oxobutyrate to react with a nitrosating agent to give tert-butyl 2-hydroxyimino-3-oxobutyrate or a salt thereof, by subjecting the tert-butyl 2-hydroxyimino-3-oxobutyrate or salt thereof to alkylation to give tert-butyl 2-alkoxyimino-3-oxobutyrate, by subjecting the tert-butyl 2-alkoxyimino-3-oxobutyrate to de-esterification to give 2-alkoxyimino-3-oxobutyric acid, by subjecting the 2-alkoxyimino-3-oxobutyric acid to halogenation to give 4-halogeno-2-alkoxyimino-3-oxobutyric acid, by allowing thus produced 4-halogeno-2-alkoxyimino-3-oxobutyric acid or a salt thereof or a reactive derivative thereof to react with a 7-aminocephalosporanic acid compound represented by the formula:



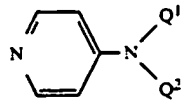
wherein R_3 and R_4 are of the same meaning defined as above, or a salt thereof to give a compound represented by the formula:



wherein R_2 stands for a halogen atom, and R_1, R_3 and R_4 are of the same meaning defined as above, or a salt

thereof, followed by allowing the said compound or salt to react with thiourea.

2. A method according to claim 1, wherein the 4-(tertiary amino)pyridine is a compound of the formula:



wherein Q^1 and Q^2 independently stand for a C_{1-6} alkyl group or combinedly together with the adjacent nitrogen atom form a cyclic amino group.

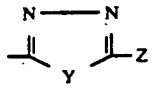
3. A method according to claim 1, wherein the cyclic amino group is piperidino, 4-methyl piperidino or pyrrolidino.

4. A method according to claim 1, wherein the 4-(tertiary amino)pyridine is a 4-(di-C_{1-3} alkylamino)-pyridine.

5. A method according to claim 1, wherein the reaction is carried out by adding diketene dropwise to a mixture of tert-butyl alcohol and 4-(tertiary amino)pyridine

6. A method according to claim 1, wherein R_1 is a C_{1-4} alkyl group.

7. A method according to claim 1, wherein R_3 is hydrogen atom; $-CH_2R_5$ wherein R_5 is hydrogen atom, hydroxyl group, mercapto group, a lower aliphatic acyloxy group having 2 to 4 carbon atoms optionally substituted by oxo, carboxyl or C_{1-4} alkoxycarbamoyl, an aromatic acyloxy group optionally substituted by hydroxyl, carboxyl. C_{1-4} alkoxycarbonylcarbamoyl or C_{1-4} alkoxycarbonylsulfamoyl, carbamoyloxy, cyano, azido, amino, carbamoyloxy, cyano, azido, amino, carbamoylthio, thiocarbamoyloxy, carbamoyloxy wherein the amino group is protected with the conventional protective group for amino, phenylglycyloxy, these residual groups of nucleophilic compounds substituted with C_{1-3} alkyl, C_{2-4} aliphatic acyl or aromatic acyl, a quaternary ammonium, or a heterocyclic thio group having a 5- or 6-membered ring containing 1 to 4 hetero-atoms selected from the group consisting of O, S and N wherein the nitrogen is optionally in the form of oxide and the heterocyclic ring is optionally substituted with one or two groups selected from C_{1-3} alkyl, C_{1-3} alkoxy, halogen, trihalogeno-substituted C_{1-3} alkyl, hydroxyl, mercapto, amino, carboxyl, carbamoyl, di-C_{1-3} alkylamino-C_{1-3} alkyl and carboxymethyl groups; halogen atom; hydroxyl, C_{2-4} alkenyl, thiol or amino optionally substituted with a substituent selected from the group consisting of C_{1-4} alkyl, C_{7-9} aralkyl, C_{6-10} aryl and C_{2-8} acyl, the substituent being optionally substituted with carboxyl, sulfo or hydroxyl group, wherein the substituted amino group may form pyrrolidino, morpholino or thiomorpholino together with the N-atom; or



wherein Y is oxygen atom, sulfur atom or an imino group optionally substituted with a C_{1-3} alkyl, C_{1-4} alkyl substituted with hydroxyl, mercapto, amino morpholino, carboxyl, sulfo, carbamoyl, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbamoyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, C_{2-4} acyloxy or morpholinocarbonyl, C_{6-10} aryl, C_{7-10} aralkyl, or C_{1-5} acyl; and Z is hydrogen atom or hydroxyl, amino, thiol, C_{1-3} alkyl, C_{7-10} aralkyl or C_{6-10} aryl group optionally substituted with a substituent selected from the group consisting of C_{1-3} alkyl, C_{1-5} acyl, C_{7-10} aralkyl and C_{6-10} aryl, the substituent being optionally substituted with carboxyl, sulfo or hydroxyl, wherein the substituted amino may for pyrrolidino, morpholino or thiomorpholino together with the N-atom.

8. A method according to claim 1, wherein R_3 is thiadiazolylthiomethyl.

9. A method according to claim 1, wherein 7β-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]3-(1,2,3-thiadiazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid is produced.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,109,131

DATED : April 28, 1992

INVENTOR(S) : Kenzo NAITO et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 15, line 14,

claim 3, line 1, change "claim 1" to --claim 2--.

Signed and Sealed this

Twenty-fourth Day of August, 1993

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

US006384215B1

(12) **United States Patent**
Deshpande et al.

(10) **Patent No.: US 6,384,215 B1**
(45) **Date of Patent: May 7, 2002**

(54) **PREPARATION OF NEW INTERMEDIATES AND THEIR USE IN MANUFACTURING OF CEPHALOSPORIN COMPOUNDS**

(75) Inventors: **Pandurang Balwant Deshpande**; **Parven Kumar Luthra**, both of Tamilnadu (IN)

(73) Assignee: **Orchid Chemicals & Pharmaceuticals Ltd.**, Tamil Nadu (IN)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/875,043**

(22) Filed: **Jun. 7, 2001**

(51) **Int. Cl.**[7] **C07D 271/08**; C07D 501/04

(52) **U.S. Cl.** **540/227**; 548/144

(58) **Field of Search** 548/144; 540/227

(56) **References Cited**

PUBLICATIONS

Salama Egyptian J Chem 24(1–3) 47–51 1982.*

* cited by examiner

Primary Examiner—Robert Gerstl
(74) *Attorney, Agent, or Firm*—Burns, Doane, Swecker & Mathis, L.L.P.

(57) **ABSTRACT**

The present invention provides new thioester derivatives of 4-halogeno-2-methoxyimino-3-oxo-butyric acid of the general formula (I), also, the invention provides a method by which the said thioester derivatives can be prepared by reacting 4-halogeno-2-methoxyimino-3-oxo-butyric acid of the general formula (II) with 2-mercapto-5-substituted-1,3,4-oxadiazoles of the general formula (III) in a solvent, in the presence of DMF/$POCl_3$ and in presence of an organic base and if desired the so obtained thioester derivatives so obtained are reacted with 7-amino-cephem carboxylic acids of the general formula (V) to produce condensed products which are insitu reacted with thiourea to get cephalosporin antibiotic compounds having the general formula (VI).

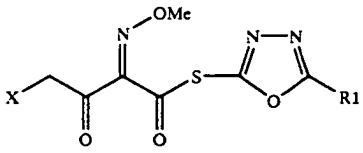
12 Claims, No Drawings

PREPARATION OF NEW INTERMEDIATES AND THEIR USE IN MANUFACTURING OF CEPHALOSPORIN COMPOUNDS

FIELD OF INVENTION

The present invention relates to novel thioester derivatives of the general formula (I) prepared by the reaction of 4-halogeno-2-methoxyimino-3-oxo-butyric acid (II) with 5-substituted-1,3,4-oxadiazole-2-thiol of formula (III). The invention also discloses the use of the new intermediate (I) for the preparation of cephalosporanic antibiotics (VI) in excellent yields and purity.

(I)



wherein

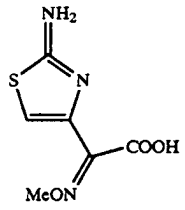
X represents halogen (Cl,Br and I)

R_1 represents C_1–C_4 alkyl or phenyl

BACKGROUND OF THE INVENTION

Acid chlorides, anhydrides, esters, amide etc. are reported in the chemical literature for activation of carboxylic acid of formula (IV). Activation in the form of acid chloride required protection and deprotection of NH_2 group.

(IV)



Activation of 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid (IV) by SO_2Cl_2/DMF is reported in U.S. Pat. No. 5,856,502 and activation of $SOCl_2$/DMF is reported in U.S. Pat. No. 5,037,988. These processes suffers with the limitation of poor by moderate yields along with the use of solvents like benzene and stringent conditions required for carrying out the reactions at commercial scale.

In U.S. Pat. Nos. 4,576,749 and 4,548,748 the acid of formula (IV) have also been activated by reacting with 1-hydroxybenzotriazole (HOBT) or 2-mercaptobenzothiazole (MBT) in the presence of dicyclohexylcarbodiimide (DCC) to produce reactive ester of the acid (IV) which reacted to cephem moiety to prepare cephem antibiotics, but the processes are time consuming and with low yields, hence not suitable.

U.S. Pat. No. 4,767,852 discloses a process for production of cephems by acylating 7-amino-3-cephem-4-carboxylic acid with 2-mercaptobenzothiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetate (MAEM). Similarly, U.S. Pat. No. 5,026,843 disclosed a process for preparing ceftriaxone disodium hemiheptahydrate by acylation of 7-amino-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3yl) thio]methyl]3-cephem-4-carboxylic acid (ACT) by using MAEM as acylating agents in good yield and quality. Thus MAEM has become the standard acylating agent for the

preparation of cephalosporins having an oximino group and a 2-aminothiazolyl group in 7-position of cephem compounds.

However, the synthesis of MAEM from 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid (IV) and 2,2'-dithio-bis-benzothiazole involves use of costly condensing agent triphenylphosphine (TPP). Moreover, during condensation of MAEM with 7-amino-3-cephem-4-carboxylic acid compound (V), a toxic compound MBT is also produced as a byproduct, see e.g., Chemical Abstracts, 111, 19243_p (1989) which is difficult to remove completely.

Thus it is evident that the procedures described in the prior art for preparation of these antibiotics are complex, involving protection, deprotection and are associated with toxic byproduct generation. Hence there is a need to develop new acylating agents which are capable of transferring the 2-aminothiazolyl moiety to cephem compounds of formula (V) in good yield but without producing this toxic byproduct. On the similar lines, a new thioester was reported by D. G. Walker, Tet. Lett. 1990, 31,6481 to acylate the cephem moiety to get cefepime sulfate but yields obtained by using this thioester were in the range of 54–73% which cannot be considered as good yield to operate a process at commercial scale. The use of this thioester was reported in the Tet. Lett. 1990, 31, 6481 only for cefepime and not for other cephalosporins. This thioester was exploited in U.S. Pat. No. 5,869,649 for making three other important cephem antibiotics.

Synthesis of 4-halogeno-2-methoxyimino-3-oxo-butyric acid is reported in Patent No. EP 0 030 294 and a large number of references are available in the patent literature disclosing the use of 4-halogeno-2-methoxyimino-3-oxo-butyric acid represented by formula (II) as the starting material. EP 0 030 294 and WO 00 0063214 discloses the condensation of the 4-halogeno-2-methoxyimino-3-oxo-butyric acid represented by formula (II) with cephem carboxylic acids by using PCl_5 Another EP Patent No. 0 842 937 discloses the formation of amide bond with cephem moiety by reacting with the thioester derivative prepared by using 2,2'-dithio-bis-benzothiazole. The preparation of this active thioester involves use of same costly condensing agent triphenylphosphine (TPP) which has been mentioned earlier in the text. Broadly the use of 4-halogeno-2-methoxyimino-3-oxo-butyric acid represented by formula (II) also suffer with almost in same disadvantages which are commonly prevalent for 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid (IV).

OBJECTS OF THE INVENTION

The primary objective of the invention is to provide new reactive thioester derivatives of 4-halogeno-2-methoxyimino-3-oxo-butyric acid of the general formula (I), which would be suitable for being used in the manufacture of cephalosporin antibiotics and would not be associated with the complexities mentioned above.

Another objective of the present invention is to provide a process for the preparation of above mentioned new thioesters (I) in good yields.

One more objective of the present invention is to provide a process for the preparation of cephalosporin antibiotics of the general formula (VI) from the said novel thioester derivatives.

Another objective of the present invention is to provide a process for the preparation of cephalosporin antibiotics e.g., cefotaxime, ceftriaxone, cefetamet, ceftiofur, cefpodoxime etc. which comprises condensation of new reactive deriva-

tives (I) with cephem compounds (V) and in situ cyclisation with thiourea to obtain targeted antibiotics(VI) in excellent yields and purity.

Still another objective of the present invention is to produce cephalosporin antibiotics that are highly pure and free from toxic byproducts.

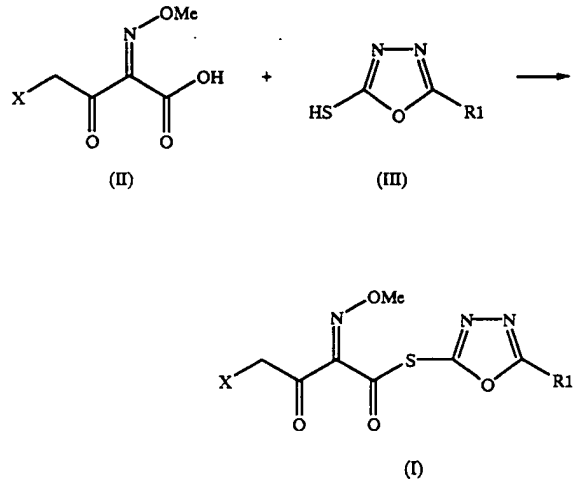
SUMMARY OF THE INVENTION

The present invention provides novel thioester derivatives of 4-halogeno-2-methoxyimino-3-oxo-butyric acid of the general formula (I) also, the invention provides a method by which the said thioester derivatives can be prepared by reacting of 4-halogeno-2-methoxyimino-3-oxo-butyric acid of the general formula (II) with 2-mercapto-5-substituted-1,3,4-oxadiazole of the general formula (III) (preparation of III, J. Am. Chem. Soc., 1955, 77, 400) by activating with $DMF/POCl_3$ in presence of an organic base in a solvent. The so obtained thioester derivatives are reacted with 7-amino-cephem carboxylic acids of the general formula (V) to produce cephalosporin antibiotic compounds having the general formula (VI).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides new thioesters of 4-halogeno-2-methoxyimino-3-oxo-butyric acid of general formula (I). The synthesis of compound (I) is achieved by preparing activated complex of 4-halogeno-2-methoxyimino-3-oxo-butyric acid (II) with $DMF-POCl_3$ followed by the reaction with thio-oxadiazoles of the general formula (III) in organic solvent in presence of an organic base at the temperature between −30° C. and +20° C. The reactive active ester is obtained quantitative yields (95–99%).

Scheme (I)



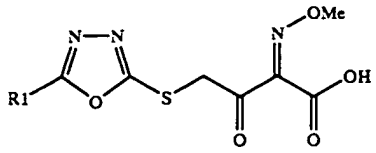
(II) (III) (I)

wherein

X represents halogen

R_1 represents C_1–C_4 alkyl or phenyl

The reactive thioester were characterized by NMR, IR and Mass spectra.



(VII)

A major side product (VII) which is formed during this reaction has also been controlled in the process. Surprisingly this side reaction has never been mentioned in the literature.

In an embodiment, in the compound of formula (I), X is chloro, bromo or iodo.

In another embodiment the organic solvent is selected from the group comprising dichloromethane, tetrahydrofuran, dioxane, N,N-dimethylformamide, acetonitrile and mixtures thereof.

In still another embodiment the organic base is selected from the group comprising triethylamine, diethylamine, tributylamine, pyridine, N-alkylanilines, and mixtures thereof.

The compound (I) so obtained is reacted with 7-amino cephem carboxylic acid of general formula (V) in two different methods and both the methods lead to same product with comparable yields and purity.

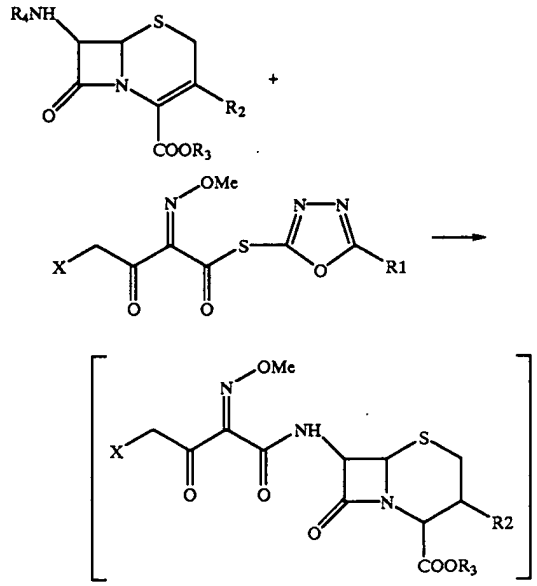
Using above mentioned thioester the cephalosporin antibiotics obtained are of high purity (90–99%). The method gives an excellent yield (70–95%) of cephalosporin without necessitating the protection of the amino group of the acylating agents, and the toxic byproduct 2-mercaptobenzothiazole is not produced.

The cephalosporin antibiotic were synthesized by following two methods:

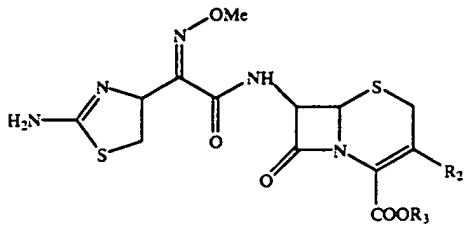
Method -I

The reactive thioester (I) was reacted with 7-aminocephem compound (V)

(Scheme II)



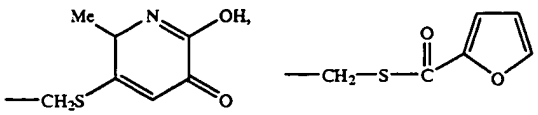
-continued



wherein

R_1 represents C_1–C_4 alkyl or phenyl

R_2 represents H, CH_3, CH_2OCH_3, CH_2OCOCH_3,



or a standard cephalosporin substituent

R_3 is hydrogen, salt or carboxylic protecting group.

R_4 is hydrogen or silyl.

In organic solvent in the presence of base to obtained condensed product, which was not isolated and is directly cyclised with thiourea in mixture of water and a polar organic solvent like tetrahydrofuran, dimethylformamide, dioxane, alcohol to obtain desired cephalosporanic antibiotics of very good purity and excellent yields.

Method -II

In this approach, starting from active ester of formula (I) final product was prepared in one pot reaction. The process comprises cyclization of active ester in the first step and in same reactor addition of amino cephem compound in mixture of water and a polar organic solvent like tetrahydrofuran, dimethylformamide, dioxane, alcohols to obtain desired cephalosporanic antibiotics of equally good purity and yields as compared to first approach. This approach provides a simple, cheap and commercially viable method without the necessity of isolating thioester and without producing any toxic byproduct namely 2-mercaptobenzothiazole.

The substituent R_2 in cephem compound (V) and (VI) represents hydrogen, methyl, acetyloxymethyl, methoxymethyl, 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1, 2,4-triazine-3-thiol, furanyl-2-carbonyl thiol or a standard cephalosporin substituents.

R_3 in cephem compound (V) and (VI) represents hydrogen, salt or a ester group which can be easily removed e.g., p-methoxybenzyl, p-nitrobenzyl, diphenylmethyl, phenacyl, trimethylsilyl etc.

In an embodiment of the present invention the organic base may be selected from the group consisting of triethylamine, N-methylmorpholine, pyridine, N-methylanilines, 1,5-diazabicyclo[4.3.0] non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 4-dimethylaminopyridine, and mixtures thereof.

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure. However, since the major characteristic feature of the present invention resides in the use of novel reactive thioester derivatives of 4-bromo-2-methoxyimino-3-oxo-butyric acid of the general formula (I) in preparing the cephalosporin antibiotics, the technical scope of the present invention should not be limited to the following examples. The following examples are provided to illustrate but not to limit the claimed invention.

EXPERIMENTAL

Example 1

Synthesis of 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-4-bromo-2-methoxyimino-3-oxo-butyrate (I).

Phosphorus oxy chloride (25.6 g) was added slowly to N,N-dimethyl formamide (12.2 g) at 0 to -5° C. Stirred for 30 minutes. Acetonitrile (200 ml) was added followed by 4-bromo-2-methoxyimino-3-oxo-butyric acid (25.0 g) and 5-phenyl-1,3,4-oxadiazole-2-thiol (19.8 g). Pyridine (44.1 ml) was slowly added to the flask at -10° C. The progress of the reaction was monitored by HPLC. After the disappearance of the starting material, the reaction mass was poured into ice-water, white colored solid separated out which was filtered and washed with water. Dried under vacuum to obtain 40.8 gm of thioester with HPLC purity (96.0–98.0%).

Melting point: 139–140° C.

^{1}HNMR (DMSO-d_6): δ4.1 (3H,s,N—O$\underline{CH_3}$), 4.3(2H,s,Br $\underline{CH_2}$CO) 7.6–7.9(5H, m, —C_6H_5)

^{13}C-NMR($CDCl_3$): δ30.2, 65.8, 121.3, 127.7, 129.7, 134.1, 147.5, 147.8, 156.3, 160.2, 186.1.

Example 2

3-Acetyloxymethyl-7-[(Z)-(2-aminothiazolyl-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylic acid (Cefotaxime acid).

Method -I

A mixture of THF (250 ml) and water (150 ml) and N,N-dimethylacetamide (25.0 ml) was stirred under inert atmosphere. At 0°–5° C., 7-aminocephalosporanic acid (25.0 g) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-4-bromo-2-methoxyimino-3-oxo-butyrate (46.0 g) were added. Triethylamine (20.4 g) was slowly added to reaction by maintaining pH 7.0 to 8.0. The reaction was checked by HPLC. After 6–8 hrs., the reaction mixture was extracted by methylene chloride(200×3). The aqueous layer is subjected for charcoal treatment. Thiourea (18.4 g) and sodium acetate (4.2 g) were added to the filtered aqueous layer and stirred for 1.0 hr to get the cefotaxime which was isolated with subsequent acidification of the aqueous layer with dil. HCl at 10° C. to pH 3.0. The solid separated was filtered, washed with water and ethylacetate and then dried under vacuum at 40–45° C. to get Cefotaxime, 40.9 g (yield 98%).

HPLC (purity)=98–99%

Method -II

2-Mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-4-bromo-2-methoxyimino-3-oxo-butyrate (46.0 g) was taken in a mixture of tetrahydrofuran (250 ml) and water (150 ml). The solution was cooled to 10° C. and the thiourea (20.47 g) and sodium acetate (4.32 g) were added. The reaction mixture was stirred for 1.0 hr. 7-amino cephalosporanic acid (25.0 g) was added followed by slow addition of triethylamine (20.4 g) the progress of the reaction was monitored by HPLC. The reaction was completed in 6–8 hr. The reaction mixture was extracted with dichloromethane (3×200 ml). The aqueous layer was acidified with dil. HCl to obtain cefotaxime, 38.0 g.

Example 3

7-[[(Z)-2-(2-Aminothiazol-4-yl)2-methoxyimino] acetamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,

2,4-triazin-3 -yl)thio]methyl]-3-cephem-4-carboxylic acid disodium hemiheptahydrate (Ceftriaxone sodium).

Method -I

7-Amino-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1, 2,4-triazin-3yl)thio]methyl]3-cephem-4-carboxylic acid (20.0 g) and 2-mercapto-5-phenyl-1,3,^{4}-oxadiazolyl-(Z)-4-bromo-2-methoxyimino-3-oxo-butyrate (27.2 g) were suspended in a mixture of THF (180 ml), H_2O (80 ml) and DMAc (30 ml) maintained at 0–1° C. under stirring. Triethylamine (11.9 ml) was added in 2–3 hours at 5° C. maintaining the pH 7.5–8.5. The reaction progress was monitored by HPLC. After the reaction was completed, the mixture was extracted with dichloromethane (3×100 ml). The aq. layer was separated and treated with charcoal (0.2 g). Thiourea (10.9 g) is added to the solution and stirred for 1.0 hr. till cyclisation is over. A solution of sodium-2-ethylhexanoate (30.5 g) in acetone was added at 10–15° C. and stirred for 1.5 hours (400 ml) of acetone was added in 1 hour at 10–15° C. to complete the crystallization. The product was filtered under N_2 atmosphere and wet cake was dissolved in mixture of water and acetone (1:2), and cooled to −10° C. Colored impurities were separated. The solution was decanted and diluted with acetone (600 ml) at 18–20° C. Precipitated solid was filtered under N_2 and washed with acetone (20 ml). Dried under vacuum at 40–45° C. to get pure Ceftriaxone sodium 25.5 g.

HPLC (purity): 98.0%

Method -II

2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-4-bromo-2-methoxyimino-3-oxo-butyrate (27.0 g) was taken in mixture of THF (250 ml) and water (125 ml). Thiourea (10.6 g) and sodium acetate (2.0 g) were added to this at 10–15° C. after 45 to 60 min. 7-Amino-3-[[(2, 5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3yl)thio]methyl]3-cephem-4-carboxylic acid (20.0 g) was suspended in the reaction mixture. The suspension was stirred for 2–3 hours at a pH of 7.0–8.5 maintained by triethylamine to get clear solution. The reaction mixture was monitored by HPLC. After completion of reaction, 200 ml water was added and pH was adjusted to 7.0. The aqueous layer was separated, charcoalized and treated with sodium-2-ethylhexanoate (30.5 g) in acetone, reaction was proceeded by same method as mentioned in Method -I to get crude ceftriaxone sodium (24.0 g).

Example 4

7-[[(Z)-2-(Aminothiazol-4-yl)-2-methoxyimino] acetamido]-3-methyl-3-cephem-4-carboxylic acid [Cefetamet].

7-Aminodiacetyloxy cephalosporanic acid (2.14 g), active ester, 2-mercapto-5-phenyl-1,3, 4-oxadiazolyl-(Z)-4-bromo-2-methoxyimino-3-oxo-butyrate(3.8 g) were suspended in mixture of THF (20 ml) and water (20 ml). TEA(1.8 g) was added slowly. The reaction was proceeded in same way as described in example II to obtain Cefetamet, 3.25 g.

HPLC (purity): 97.0%

Example 5

7-[[(Z)-2-(Aminothiazol-4-yl)-2-methoxyimino] acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid [Cefpodoxime acid].

7-Amino-3-methoxymethyl-3-cephem-4-carboxylic acid (24.2 g) and 2-mercapto-5-phenyl-1,3 ,4-oxadiazolyl-(Z)-4-bromo-2-methoxyimino-3-oxo-butyrate (39.7 g) were suspended in 400 ml of THF and water mixture (1:1). At 10° C. TEA added to maintain pH 7–8. The reaction was monitored and proceeded as described in example II (Method-I). The pH was adjusted to 2.7 using 16–18% sulphuric acid. Solid was cooled to 10°° C., filtered and washed with water (3×50 ml) and finally with acetone (20 ml) to obtain the Cefpodoxime acid, 37.5 g (yield 88%).

HPLC (purity) 98.0%

Example 6

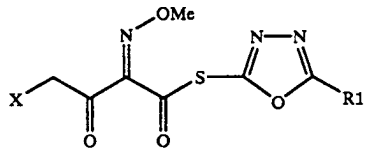
7-[[(Z)-2-(Aminothiazol-4-yl)-2-methoxyimino] acetamido]-3-(furanylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (Ceftiofur).

7-Amino-3-[(2-furanylcarboxyl)thiomethyl]-3-cephem-4-carboxylic acid (3.4 g) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-4-bromo-2-methoxyimino-3-oxo-butyrate were added to a mixture of THF (35 ml) and water (35 ml) at temperature 5° C. The pH of reaction was maintained at 7.5 to 8.5 by addition of TEA during the reaction. After completion of reaction, the reaction was extracted with methylene chloride (25 ml×3). The aqueous layer was diluted with 15 ml THF and thiourea was added to the aqueous and stirring was continued for 30 to 45 min. to complete the cyclisation. After that pH was lowered to 3 by addition of 1N HCl. The solution is saturated by salt. The organic layer was separated and pH was further adjusted to 0.5 by concentrated HCl. IPE (250 ml) was added to precipitate the hydrochloride salt of Ceftiofur, 4.3 g (yield 75.0%).

HPLC (purity): 98.0%

What is claimed is:

1. A novel 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-4-bromo-2-methoxyimino butyric acid derivative used in the preparation of cephalosporin antibiotics, and represented by formula (I)



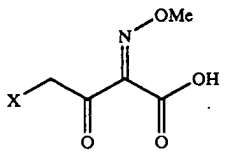
wherein

X represents halogen (Cl, Br and I)

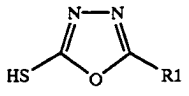
R_1 represents C_1–C_4 alkyl or phenyl.

2. A process for preparing active thioester derivatives represented by formula (I), said process comprises the step of reacting 4-halogeno-2-methoxyimino-3-oxo-butyric acid represented by formula (II)

(II)



(III)



wherein X represents halogen (Cl,Br,I)

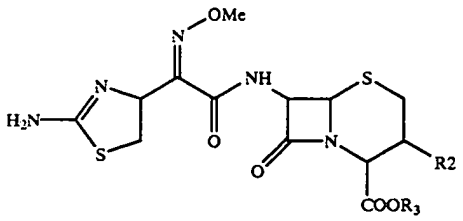
wherein R_1 represents C_1–C_4 alkyl or phenyl with thiooxadiazole of formula (III) in the presence of DMF, phosphorous oxychloride, an organic base and a sol-

vent at temperature being maintained in the range -30° C. to +20° C.

3. A process as claimed in claim 2, wherein the organic solvent is selected from the group comprising dichloromethane, tetrahydrofuran, dioxane, N,N-dimethylformamide, acetonitrile and mixtures thereof.

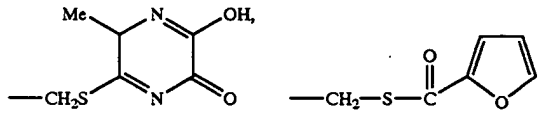
4. A process as claimed in claim 2, wherein the organic base is selected from the group comprising triethylamine, diethylamine, tributylamine, pyridine, N-alkylanilines, and mixture thereof.

5. A process for preparing a cephalosporin compound of formula (VI)



wherein

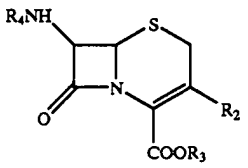
R_2 represents H, CH_3, CH_2OCH_3, CH_2OCOCH_3,



or a standard cephalosporins substituent,

R_3 is hydrogen, salt or carboxylic protecting group and R_4 is hydrogen or silyl, said process comprising the step of reacting a compound of formula (V) with a compound of formula (I) and thiourea

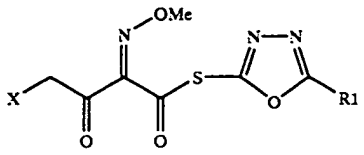
(V)



wherein

R_2, R_3 and R_4 are defined as above

(I)



wherein, X & R_1 are as defined above.

6. A process for the preparation of cephalosporin compounds of formula (VI) as in claim 5 comprising reacting a compound of formula (I) in a mixture of an organic solvent and water with a compound of formula (V) in the presence of a base at a temperature in the range of 0° C.-30° C. preferably at 15° C., wherein the intermediate which is formed insitu is treated in same reactor with thiourea to obtain compounds of formula (VI).

7. A process for the preparation of cephalosporin compounds of formula (VI) as in claim 5 comprising the step of reacting thiourea with compound of formula (I) in mixture of an organic solvent and water in the presence of base at a temperature in the range of -5° C. to 30° C. preferably at 15° C. followed by the addition of a compound of formula (V) with at pH between 7-8.5 maintained by addition of a base to obtain the cephalosporin compounds of formula (VI).

8. A process as claimed in claim 5, wherein R_2 is hydrogen, methyl, methoxymethyl, acetyloxymethyl, (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio methyl, furylcarbonyl thiomethyl or a standard cephalosporin substituent.

9. A process as claimed in claim 5, wherein R_3 is or alkali metal salt.

10. A process as claimed in claim 6 or 7, wherein the reaction is effected in the presence of water and an organic solvent selected from the group consisting of tetrahydrofuran, N,N-dimethylacetamide, N,N-dimethylformamide, dioxane, acetonitrile and mixtures thereof.

11. A process as claimed in claim 6 or 7, wherein the reaction is performed in the presence of an organic base selected from the group consisting of triethylamine, N-methylmorpholine, pyridine, N-methylanilines, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2] octane, 4dimethylaminopyridine and mixtures thereof.

12. A process as claimed in claim 6 or 7, wherein said compound of formula (VI) is a syn isomer.

* * * * *